COLLABORATORS IN FIRST AND SECOND EDITIONS

Herman Beerman, M.D.
John H. Besancon, M.D.
Frank E. Cormia, M.D.
Vaughn C. Garner, M.D.
William H. Goeckerman, M.D.
Franklin A. Ireland, M.D.
Charlotte B. Jordan, M.D.
Allen D. King, M.D.
George V. Kulchar, M.D.
Paul A. O'Leary, M.D.
Donald M. Pillsbury, M.D.
Arthur G. Schoch, M.D.
Loren W. Shaffer, M.D.
Cleveland J. White, M.D.

Reprinted April, 1944, and November [illegible]

INTRODUCTION TO THE THIRD EDITION

With this edition, MODERN CLINICAL SYPHILOLOGY almost attains its majority (1926–1944). The first edition was a personal write-up in the days of American syphilology's youth. The second edition was a cooperative enterprise within the Pennsylvania group, aiming at an evaluation of the whole syphilologic field. The third edition, confronting the maturity of American syphilology and its preeminent contributions, has ceased to be an affair even for one-man guidance, and has become a full-fledged near-encyclopedic collaboration. It is not possible to separate, itemize or initial the individual contributions of Stokes, Beerman, Ingraham and their associates.

The original purposes of MODERN CLINICAL SYPHILOLOGY have been adhered to—to produce a single-volume, comprehensive summation of diagnosis and treatment, vivid and readable as well as factually authoritative and up to date, complete to within the well-known 99.44 per cent purity standard and reasonably reflective not alone of the authors' views but of the literature. We have been repeatedly urged to incorporate full bibliographic references. This is impossible in one volume. And the fate of two-volume works is that they reach only the desks of specialists, whereas *syphilis is a practitioner's problem.* We have, however, in the third edition, given references of the past ten years à date in parentheses to aid in consulting the standard bibliographic works. The enormous increase in syphilologic knowledge, especially of treatment, and the earthquake of penicillin have made the revising of a book at this moment a hazardous undertaking. We are convinced, however, that old and new must mingle for another ten years before the arsenicals pass, perhaps with late and even early syphilis, into limbo. The principles have a touch of the immortal, though the facts shift and change.

The critical need for condensation to meet increasing costs and scarcities has had to face the inescapable expansion of the subject. The book is a genuine tribute to the generosity of the publishers and their many ingenuities in the technic of their craft. The book unavoidably contains much fine print, and omits some matter, referring the reader to previous editions. We plead in extenuation of length and fine print that it also contains a great deal of information—so much that the authors might justly quote Herbert Spencer when he said that no man is the equal of his book. The attempt to write simultaneously for the student, as illustrated in the summaries and the principles for the practitioner, as illustrated in details and cases, and for the expert, as shown by the discussions and references to the literature, really telescopes three books into one.

Approximately 75 per cent of the text has been rewritten. The penicillin chapter and the account of syphilis in public health and military medicine are new. The chapter on prenatal, now largely called congenital syphilis, has been expanded and rewritten. The progress of serologic diagnosis, forward and backward so to speak, has been reflected in extended space devoted to the biologic false-positive reaction, so disturbing to doctor and patient these days. Every important technic of treating syphilis gets, we believe, full detailed and practical discussion. The final chapter on the detoxicants and

penicillin represents the first textbook summation of which we know that makes accessible information on this agent in the field of syphilotherapy It is a privilege to acknowledge the generosity with which the giants in the exploratory field like Mahoney and Moore, have made their thinking and results accessible to us. We have a few of our own co-workers to whom also we point with pride. The Penicillin Panel of the Venereal Disease Subcommittee and the Committee on Chemotherapeutic and Other Agents, with the Committee on Medical Research of the National Research Council have released information to us literally up to the last minute of the publishing deadline. The Journal of the American Medical Association has been similarly generous in permitting extended quotation of recent papers The courtesies of many others are specifically noted

Previous editions have not failed to draw criticism both for too many words in general and too few or none about something in particular We hope comment and criticism of this sort will continue—to keep us on the alert. The subject index of the third edition is by Stokes, who hereby assumes responsibility The Secretary of the Department of Dermatology and Syphilology and the Institute for the Control of Syphilis, Miss Virginia MacElroy has contributed greatly by ingenuity and meticulous accuracy to the many text summaries, the manuscript and the index

The inspirational closing sentence does not easily come to us. We may perhaps take comfort and courage however in the way in which a book like this records the impending extinction of a centuries old plague in the short space of two decades and reflects the advance in mankind s most noble war—the battle to achieve the ideal— *Mens sana in corpore sano*

PHILADELPHIA, PA.

JOHN H STOKES
HERMAN BEERMAN
NORMAN R INGRAHAM JR.

CONTENTS

TABLE OF ABBREVIATIONS

A_2	Aortic second sound
Ars. or AB	Arsphenamine
B. M. R.	Basal metabolic rate
Bi	Bismuth
B. P.	Blood pressure
BST	Blood serologic test
BWR	Blood Wassermann reaction
CCG	Cooperative Clinical Group
CNS	Central nervous system
Coll.	Colloidal
CSF	Cerebrospinal fluid
CSF WR	Spinal fluid Wassermann reaction
CV	Cardiovascular
Gold sol	Colloidal gold
Hg	Mercury
KI	Potassium iodide
L. H.	Lues hereditaria
Lues I (or L. I)	Primary syphilis
Lues II (or L. II)	Secondary syphilis
Lues III (or L. III)	Late syphilis
MCS	Modern Clinical Syphilology ed. 2
M. M.	Mucous membranes
NaI	Sodium iodide
Neg.	Negative
Neo	Neoarsphenamine
Nonne (or N.)	Globulin test
P_2	Pulmonic second sound
Pos.	Positive
Sars	Sulpharsphenamine
SWR	Serum Wassermann reaction (blood)
WR	Wassermann reaction
+++	3 plus (positive)
V	Used in the Index to imply discussion of differential diagnosis

Modern Clinical Syphilology

CHAPTER I

THE FUNDAMENTAL BACTERIOLOGY PATHOLOGY AND IMMUNOLOGY OF SYPHILIS

The syphilology of the nineteenth century was fundamentally clinical that of the first three decades of the twentieth century has found its inspiration primarily in the laboratory under the presiding genius of Schaudinn of Metchnikoff and Roux of Bordet and Wassermann of Neisser of Ehrlich

Underlying the tremendous advances of modern treatment are of course, fundamental experimental contributions. Complex and difficult though the fields of experimental reasoning and observation may appear to the onlooker it is here unhesitatingly urged upon every student of syphilis that a systematic and earnest effort be made to grasp such part of the fundamental principles underlying the clinical behavior diagnosis and treatment of syphilis as may be introduced into a work of this kind No one who has had even a limited experience in answering the questions on which students and physicians seek information in their practical contacts with the disease can fail to realize that the great ailment of modern syphilological practice is a lack of comprehension of the why and wherefore rather than the "what to do.

A Definition of Syphilis.—Syphilis is an infectious disease due to *Spirochaeta pallida* of great chronicity systemic from the outset capable of involving practically every structure of the body in its course distinguished by florid manifestations on the one hand and years of completely asymptomatic latency on the other· able to simulate a large proportion of the entities comprising the field of medicine, surgery and the specialties transmissible to offspring in man transmissible to certain laboratory animals and treatable to the point of presumptive—but not, thus far demonstrable—cure by the use of derivatives of arsenic mercury bismuth the iodides and nonspecific or fever therapy To this range and to this essentially Machiavellian facility in disguise deceit and malevolence we owe an interest in syphilis among medical and scientific men everywhere which is all but unique and which is the mainspring of much of the progress already made against it.

SPIROCHAETA PALLIDA

Fritz Schaudinn, the parasitologist, assisted by the syphilologist F Hoffmann, identified in March 1905 the spiral organism which is today accepted as the cause of syphilis from an unstained specimen with a relatively low-power microscope without darkfield The succession of organisms credited briefly as responsible since the disease was first recognized as an infection and the fascinating story and reasoning underlying the life cycle concept are excellently reviewed by Ingraham (1932) The term "*Spirochaeta*

pallida supported by clinical usage is here employed in preference to the more exact but less familiar term "*Treponema pallidum*" of the laboratory

The inter-relations among spirochetes include many points of importance for comprehension of the biology of syphilis. Bessemans (1936) points out that morphologic differences among spiral organisms are less important than functional or pathogenetic differences. *Spirochaeta pallida*, *Spirochaeta pertenuis* (yaws) and *Spirochaeta microdentium* (a mouth saprophyte sometimes credited with producing gingivitis) resemble each other very closely There is evidence that the spirochete of yaws (*Sp. pertenuis*) produces an infection which sometimes protects against syphilis (Turner (1936) Chesney (1934)) Kolmer and Eagle believe that the Reiter spirochetal antigen which is quite effective in a complement fixation test for syphilis (Pallgen) contains not *Spirochaeta pallida*, but *Spirochaeta microdentium*.

Bessemans lists differences in virulence and behavior between *Spirochaeta pallida* in lymph nodes as compared with the same organism in the testicles of rabbits. He believes that the brain-



Fig. 1 —*Treponema pallidum* in orchitis Stained by Levaditi method (× 1000) (Collection of Dr Noguchi.)

accustomed *Spirochaeta pallida* of paresis has lost its virulence for animals; mentions six other evidences that there are functionally different varieties of *Spirochaeta pallida* under common or very slightly variable morphology Bejel which Hudson (1936) maintains is the yaws-like mild form of syphilis among the Bedouins is thus interpretable (Bessemans) as a functional variable of morphologically constant spirochete. Morphology thus becomes critical chiefly in the differential elimination in the darkfield of saprophytic spirochetes that may be confused with *Spirochaeta pallida*. These include especially mouth spirochetes (*Spirochaeta buccalis*, *Spirochaeta intermedia* or *macrodentium*, and *Spirochaeta dentium* or *microdentium*) The larger types include also *Spirochaeta vincenti* The genital types whose differential morphology must be studied, include *Spirochaeta refringens*, *Spirochaeta calligyrum*, and *Spirochaeta cuniculi* of rabbits, whose confusion with "thick" form of *Spirochaeta pallida* betrayed Levaditi and Marie (1923) into the first fallacious morphologic description of neurotropic strain of *Spirochaeta pallida*. *Spirochaeta cuniculi* produces easily distinguishable lesions in the rabbit, and is not pathogenic for man. While some confusion has undoubtedly been introduced into the earlier experimental work on rabbits by the non-recognition of *Spirochaeta cuniculi* infection, Nichols and Walker believe that this need not be greater or more significant than that introduced into the study of tuberculosis

by the existence of other acid-fast organisms such as the smegma bacillus. Pinta, formerly regarded as tropical cutaneous mycosis, is apparently produced by spirochet indistinguishable morphologically from *Spirochaeta pallida* (Saenz, Gra Triana and Alfonso Armenteros (1938), Pardo-



Fig 2.—*Spirochaeta pallida* as seen with the electron microscope lth t lateral protrusions, one of hich is show very clearly t be made up of small spherical bodies. Meserow sky observation that stalk often carries more tha one minut bud led him t conclude that the buds have the property of dividing (Stral P190B (88a) × 14,000.) (From H. E. Morton nd T F Anderson Am. J Syph., Gonor and Ven. Dis. 26 563 1942.) (Courtesy of Dr Harry E. Morton.)



Fig. 3.—A view of *Spirochaeta pallida* under the electron microscope showing continuous envelope or membrane also end knob (From U J Wile, R. G Picard, and E. B Kearny J.A.M.A. 119 880 1942.) (Courtesy of Dr Udo J Wile)

Castello et al. (1938 and 1940)) (See Beerman, 1943) In clinical syphilologic practice the mouth spirochetes present very much more difficult differential problem than any other and one which greatly increases the uncertainties in darkfield diagnosis of mucous membrane lesions. Differential details are discussed under darkfield and staining.

Morphology —Schaudinn s original description of *Spirochaeta pallida* is still accepted today as in Ingraham s review (1938) "The length varies from 4 to 10 micra, the average being about 7 micra, as shown in comparison of the spirochetes with the blood corpuscles in their midst. The number of windings varies from 3 to 12 (Schaudinn later admitted a limit of 14 and finally of 26) The average number has been shown repeatedly to be between 6 and 14 The organism is seldom if ever more than 0.25 μ in thickness The average relation of width of spirals to length of turns is 1:2 Schaudinn, in his original description was able to define not only a certain amount of structure but to recognize the (double) flagellum at each end of the organism As revised by the recent descriptions of *Spirochaeta pallida* by Morton and Anderson (1942) and by Wile Pickard and Kearny (1942) using the electron microscope (it must be recalled that this is a dry preparation of *Spirochaeta pallida*) the primary spirals have a width of from 0 4 to 0.55 μ with a pitch of about one μ. Initial constriction of the spirochetal body suggests the beginning of transverse division, leading eventually to two spirochetes held together by a tenuous filament which may be the unstained segment observed by other workers in stained preparations. After the separation of the two spirochetes at this point the thin filament may persist as the frequently observed terminal filament.

Amorphous material has been found about the spirochetes in certain preparations This is not to be confused with the flagella like filaments, or tendrils (Wile and Kearney 1943) projecting from the sides of the organism or with the terminal filaments which appear to be definite structures. Dense spherical bodies are frequently observed within the bodies of the spirochetes Similar but larger dense spheres are also observed to protrude from the body to be attached by a stalk, and to appear as clusters attached to the body or separated from it. Such clusters were also described by Mierowsky (1913 1941) Ingraham (1938) remarked on the prolonged discussion which has resulted from distortions of form and groupings of spirochetes in their possible relation to the mode of reproduction Manouélian (1940) states that the organism divides transversely into two, three or four parts, each of which represents a new organism or a granule may be detached from the body of the spirochete by the same process of transverse division These granular forms remain attached to the spirochete by means of a filament, which with the granule finally breaks away from the organism. Atypical granular forms are often found in the lesions of syphilis, such as gummas aneurysms, and lesions of early congenital syphilis They are also found in early lesions after antisyphilitic treatment. *Spirochaeta pallida* has a highly characteristic motility analyzable into three elements a motion of translation in the direction of the long axis a slower revolution or rotation of the spiral like a corkscrew on its own axis, and a waving or twisting motion from side to side The notable and distinctive characteristic of the organism which will be mentioned later is its ability to hold the coil of a spiral without wave motion or flattening

A warning should be given all students of the morphology and behavior of *Spirochaeta pall d* f the ever-present pitfall of artefact. Imitations of spirochetes capable f deceiving the inexperienced and even usable for teaching purposes, l been described by Eberson, and a formula for the preparation of artific al spirochetes has recently been devised

Life Cycle and Involution Forms.—The question of the life cycle of *Spirochaeta pallida* under discussion since Schaudinn's original studies, still remains in an unsettled state. Students of the problem should read in full Ingraham (1938) on the subject, and Olsen (1938) and should include of course the observations of Warthin and Starry, Saleeby and Greenbaum, Levaditi, Manouélian, Bessemans (1936). The practical interest of the question concerns of course the existence of a resistant form of granular or ultramicroscopic type, capable of being concealed within so small an object as the spermatozoon or the virulent pulp of apparently spirochete-free lymph nodes. O'Farrell and Balfour connected the shedding of granules by *Spirochaeta pallida* and *Spirochaeta refringens* with the action of 606. Ringed forms have also been given involutional importance in tissue and Olsen mentions as a special type the small form of *Spirochaeta pallida* observed in syphilitic aortic lesions. Noguchi succeeded in demonstrating the really remarkable range of confusion possibilities among spirochetes which must constitute a possible pitfall in any diagnosis or reasoning based purely upon cultural or involution characteristics. Kendall has shown that certain microorganisms, including the *Spirochaeta icteroides* (yellow fever) can by suitable nutritive conditions be passed through an ultramicroscopic state.

Cultivation of Spirochaeta Pallida and the Laws of Koch.—The situation to date (1943) can be summarized by the statement that all the laws of Koch have been satisfied except that of cultivation of virulent *Spirochaeta pallida*. Competent observers have repeatedly claimed success in this undertaking, but confirmation has been unsatisfactory. Gammel and Ecker (1931), and Kast and Kolmer (1940) rated the problem as still unsolved. It should be recalled that cultivation of the organism and cultivation of the virulent organism are two distinct undertakings. Schereschewsky in 1909 is now generally credited with having been the first to cultivate the organism successfully. Wile and Snow (1941) applied the chorio-allantoic membrane of the chick embryo technic to the problem with what they regard as two successful experiments. They were unable to demonstrate spirochetes in the infectious chick tissue and compare their findings in this particular with the absence of organisms in the infectious popliteal lymph nodes of rabbits and the viscera and brain of the mouse. Sterzi and Staudecher (1939) used the chick embryo method unsuccessfully. Loren Shaffer showed that it was possible definitely to increase sometimes enormously the number of *Spirochaeta pallida* in tissue removed from syphilitic animals by anaerobic incubation for from forty-eight to seventy-two hours.

Experimental Syphilis in the Animal.—The study of experimental syphilis in the animal, despite its limitations, has made possible the advances of the twentieth century as contrasted with the clinical era of the nineteenth. The work of Metchnikoff and Roux and the epochal studies of Neisser, many of which have been merely repeated by subsequent investigators were undertaken on the ape, necessitating in Neisser's researches a completely equipped scientific expedition to Java, in order to tap an adequate reservoir of animal material. Finger, Uhlenhuth, Mulzer, Brown and Pearce and Chesney, Kolle, Levaditi, Kolmer and Truffi are perhaps the senior immortals in the contributions made by experimentation in the rabbit. Schlossberger, Turner, Kemp, Rakies and Severac, Klauder, Beerman, Greenbaum, Bessemans, Brandt, Eagle, Parner are representatives of the most recent developments. To the study of the disease in the rabbit the clinician owes what conception he has of the influence of age, sex, constitution, season, infective dose of organisms, diet and endocrine activity on the course of the disease. The conceptions of the asymptomatic carrier have been greatly expanded by Kolle and his successor Schlossberger not only through the study of asymptomatic infection in rabbits, but its practically unvarying occurrence in the mouse, which following Schlossberger and Rankes and Severac's exploration of the possibilities, has provided the means not only to modify the characteristics of the organism with respect to tropism for such structures as the nervous system, but also to provide an invaluable biological filter through which a new strain of organism can be passed from man to the rabbit. The influence of site of inoculation on the course of the syphilitic infection is an animal contribution; the demonstration of the successive barriers of defense and fields of reaction in the body tissues are products of animal studies. For the chemotherapeutic attack upon syphilis, the experimental animal has provided much, though less than might have been hoped for. As the toxicity test-tube so to speak, with trypanosomes for index purposes, the mouse has supplied the modern chemotherapeutic indices, slowly replaced by the study of spirochetal effects and cure in the rabbit. If anything, there has been something of a tendency to overdo the transfer of toxicity and chemotherapeutic effect as worked out in animals to the anticipated behavior of drugs in man. It is now clear that there are important and in fact, the most important, groups of toxicity reactions in man which have no homologues in animals and in which animals cannot be used to predict the clinical effect. The effect of trauma on the localization of syphilitic lesions, incontestably established for animals as for man, still remains, as far as mechanism is concerned, an unsolved riddle. It deserves to be emphasized that animal syphilis is the domain of experts and that confusion and inadequacy await the inexperienced in their efforts to transfer the human

infection to the animal experimental subject. The technic of animal inoculation described in previous editions is therefore now omitted, and those whose clinical opportunities bring them valuable strains of resistant or biologically distinctive syphilitic infection for study should immediately seek the aid of one or another of the recognized experts in the animal field, rather than to attempt animal inoculation for themselves.

Sub-varieties or Strains of Spirochaeta Pallida.—While abundant question has been raised as to the identity of the cultured *Spirochaeta pallida* with *Spirochaeta pallida* of human syphilis, no reasonable doubt remains as to the identity of the organism associated with animal syphilis and the *Spirochaeta pallida* in the syphilis of man. In fact, the crucial demonstration of the infection of human laboratory workers with syphilis by *Spirochaeta pallida* being carried in rabbits has several times, unfortunately been made (Wakerlin, Shaw 1941) The Nichols and the Truffi strains have now been carried in animals to the point where they may be regarded as having positive identities. A number of less well-known strains are used in Europe. Neurotropism, the first pathogenetic functional peculiarity to attract attention as a strain characteristic, has now been traced through the work of Schlossberger and of Raiziss and Severac, to the important biological principle that prolonged residence in type of tissue or environment is capable of developing tropism and adaptation in *Spirochaeta pallida*. Thus, sojourn in the brain tissue of



Fig. 4.—Typical chancres of the rabbit testes. (Collection of Drs Brown and Pearce.)

mice, has been shown to prepare the Nichols strain of *Spirochaeta pallida* for the development of neurotropic reaction in the rabbit. Kolle and Schlossberger pparently succeeded in carrying the differentiation of strains and the detection of strains of greater and lesser virulence in animals by immunologic methods to the point where a superinfection ith second strain could be produced in given animal, and the original strain and the superinfecting strain subsequently recovered and identified by animal reinoculation. Kritschewsky demonstrated strain characteristics for *Spirochaeta recurrens*. Beerman and Severac have been fortunate in maintaining an arsphenamine-resistant strain of *Spirochaeta pallida* recovered from treatment-resistant patient, through 87 generations (1936 1938, 1942)

For the clinician these observations have as yet little clearly defined meaning. Strain characteristics and tropism have been suspected in conjugal tabes and paresis in which husband and ife infected by the same organism (presumably) developed the same manifestations of the disease. Famous examples of neurotropism in hich 5 or more persons infected by the same woman all developed paresis, are cited in Chapter XX. Dermotropism as opposed to neurotropism has been a much labored conception in clinical as ell as experimental syphilology I Wile and Belote study of this question the histologic and pathogenetic differences between the alopecia associated ith presumptive neurotropism and the follicular infiltrative syphilid

are well brought out. It cannot unfortunately be said that clinical conceptions of syphilis have thus far derived much from the experimental investigation of strains.

Rate of Invasion, Route of Distribution, Identification of Spirochaeta Pallida in Body Tissues and Fluids.—Granted that the conditions prevailing in the experimental infection of animals by direct exposure of the intact body surface to *Spirochaeta pallida* are comparable to those in man, Mahoney and Bryant (1933, 1934) have apparently determined under the best control conditions that *Spirochaeta pallida* invades the genital mucosa (rabbit prepuce) between the third and fourth hour after the organisms are placed on the surface. Soap and water cleansing and other forms of disinfection conveyed protection against infection in exposures as long as two hours, but not as long as three hours. Strong antiseptics including alcohol and iodine, were somewhat more effective up to three hours, but useless thereafter. Ko (1933) was unable to demonstrate infection through the uninjured skin of mice. The literature on the rate of invasion of the lymphatics and blood stream by spirochetes gaining entrance from inoculated fragments of tissue, intratesticular injections and so forth is reviewed by Raiziss and Severac (1937), the shorter



Fig. 5.—Twin chancres in man, produced by contact inoculation. The two lesions can be exactly superposed.

periods range from one-half, one, two, seven, and twenty-four hours after inoculation, up to the time of recognition of organisms in the adjacent lymph nodes. Kolle and Evers (1926) were able to demonstrate the presence of spirochetes in lymph nodes of guinea pigs five minutes after inoculation. The traumatic quality of many of these inoculation experiments must of course be recognized. Tani, Ogiwara, Hatakeyama and Oya (1933) found that spirochetes rubbed into scarifications in the scrotums of rabbits appeared in the inguinal nodes within five minutes and in the blood in an hour. It is evident, therefore, that where trauma of any description paves the way, dissemination of the infection is exceedingly rapid, and the disease is indeed systemic from its very inception. Observations such as these have the clinical significance of doing away with long practiced excision of the chancre in the effort to remove the local, supposedly isolated, focus of spirochetes at the onset of the disease. Levaditi, Vaisman and Rousset-Chabaud (1936) grafted bits of rabbit testicular syphiloma on the backs of mice which were killed at intervals of from two to forty-two days. Histologic study of inoculated areas showed that spirochetes had entered the neighboring lymphatics by the second day; by the forty-second day there was a generalized infection of the lymphatic system. Spirochetes are also present in the walls of the blood vessels

of the infected region on the first, third and fifth days and blood from infected mice was infectiou for rabbits, one three t lve and thirty-five days.

Tw routes of distribution of the organism are clinically important distribution by way of the lymphatic system and distribution by way of the vascular system Both are discussed under elective localization. *Spirochaeta pallid* has been identified in the normal skin of persons with early syphilis (primary and secondary) (Frankl, 1930 nd Charpy 1937) Charpy identified the organism in lymph from scarified sit on the mucous membrane of the glans penis before the development of the chancre. Levaditi, Storesco and Vaisman (1936) on the other hand found that very little dispersion of organisms from the skin took place in experimental animals and ma Frazier and H (1933) demonstrated the presence of *Spirochaeta pallida* in tumor histologicall diagnosed subcutaneous sarcoid of Darier Roussy in a Chinese patient ith syphilis. Among other tissues in which *Spirochaeta pallida* is easily and quickly identified following infection should be mentioned the testis, spleen and bone marrow as originally established by Neisser Javanese work, the organisms appearing t these sites within twenty-four hours after inoculation. It should not be forgotten that the identification of spirochetes in tissue as reported for example by Freedburg and Barron (1940) in the human gastric mucosa by no means establishes their identity as *Spirochaeta pallida*. The experimental work in seminal transmission of syphilis has run foul of failure t control this factor of error according to Parlser (1940–1942) recent critique. Morphologic differentiation of organisms must be confirmed by experimental inoculation and distribution studies t validate the findings. Thus Dormanand Sahyun (1937) identified what they believed t be morphologically typical *Spirochaeta pallida* in foci conforming to Warthin descriptive criteria, but the confirmation of the identity of the organism remains nonetheless incomplete. Kemp and Rosahn (1937) by intravenous injection of spirochete emulsion in rabbits secured inoculation of placentae yet the placenta proved to be absolut barriers to the infection of the rabbit fetuses. The fact that the distribution of *Spirochaeta pallid* through tissue barriers is not merely matter of inoculation or contact, was interestingly demonstrated by Raison and Severac, who found that inoculation of the organism into the cerebral ventricles of rabbits resulted in the development of testicular hancre rather than direct inoculation of the adjacent nervous system tissues nd meninges. The belief that such shortening of the rout of invasion occurred in inoculations about the face hich were supposed to lead to an increased incidence of cerebral syphilis has not been established Wagner (1931) failed to demonstrat any direct passage of an experimental infection on the rabbit cornea to the tissues of the adjacent nervous system.

Of the body fluids, the blood contained the organism, according to Frazier and Pian recent review (1930) as early as twenty days before the appearance of the chancre in Chinese male blood donor Moore (1933) observed two cases in which the blood was proved to be infectious during the seronegative primary stage. The animal experimental evidence indicates (Brown and Pearce, 1920) that 0.5 cc. of blood one week following intratesticular inoculation, will transmit infection t normal rabbits. Raison and Severac demonstrated the appearance of spirochetes in the blood after intratesticular inoculation in as short period as five minutes. Uhlenhuth and Mulzer (1913) and Früh ald showed that the blood in the primary stage of syphilis, transmits the disease in 81.2 per cent of cases, nd in secondary syphilis, in 75 per cent of cases. Frühwald and number of other observers have confirmed fully the infectiousness of the blood in the seronegative primary phase of the disease Frühwald also demonstrated the infectiousness of the blood in latent syphilis. I contrast, and illustrating the range of variation which must be allowed for in clinical generalization, particularly involving blood transfusion, McNamara was forced by circumstances to use the blood of six lat syphilitic Negroes in nineteen transfusion for ten recipients, and as unable to demonstrate single transfer of the syphilitic infection under such circumstances. The entire problem of syphilis transmission by blood transfusion will be subsequently discussed. The clinical principles involved may be tersely st ted no recent advances such as the demonstration of protection afforded b admixture of blood or serum with the arsphenamines alters the clinical principle that to use the blood or serum, cerebrospinal fluid or tissues of person know t have had syphilis, in any form of biological treatment in ma without adequat sterilization and without the fullest practicable precautions against the presence of syphilis in the donor is reprehensible

Th cerebrospinal fluid is know t contain *Spirochaeta pallida* under variety of circumstances. Nichols and Hough est blished the famous Nichols-Hough strain of *Spirochaeta pallida* in rabbits from the cerebrospinal fluid of patient ith early acut neurosyphilis Geiger found the organism in the fluid of tw cases of seronegative primary syphili It has been repeatedly found in the spinal fluid of syphilitics in hom the cell counts, globulin content, Wassermann reaction and colloidal test ere negative A summary of the reports in the literature indicates that the organism may be recovered in from 15 per cent t 40 per cent of normal spinal fluid

in early syphilis. Pearce H and Mu (1936) report very interestingly their failure to demonstrat *Spirochaeta pallida* in the cerebrospinal fluid of forty-two syphilitic Chinese patients. In Chesney and Kemp cited series (1924), special precautions were taken to void confusion with *Spirochaeta recurrentis*.

Saliva apparently contains *Spirochaeta pallida* only when syphilitic lesions are present in the mouth or throat. Animal experimental confirmation of this negative finding has most recently been furnished by Barnett and Kulchar (1939).

The finding of spirochetes in urine sediment is good illustration of the care that must be taken in excluding the possible presence of other *Spirochaeta pallida* in body secretions. Pariser (1944) points out that Stoddard, Patterson, Felsinger nd Huber and he himself have found spirochetal forms in urethral secretions which can be confused with *Spirochaeta pallida*. *Spirochaeta pallida* may also of course be present i rine from syphilitic lesions along the urinary tract, and particularly the urethra.

The presence of *Spirochaeta pallida* in semen has apparently been established by succession of investigations, beginning ith Finger Neisser and Uhlenhuth and Mulzer the source of the spirochetes ho ever seems t be the real question at issue Pariser (1942) in an extended and carefully controlled study of the infectiousness of semen in which the presence of spirochetes from urethral and genital lesions was as completely excluded as possible was unable t obtain positive inoculation. I other words, *Spirochaeta pallida* in semen is present therein by virtue of syphilitic lesions in the urethra or along the urogenital tract and not because it is present in semen as secretion. This would seem t set t rest, if confirmed, the belief that there is a rest form of *Spirochaeta pallida* capable of being carried in the sperm or semen and capable of transmitting the disease to the ovum instead of t the fetus through the mother Kemp has established for lat syphilis (1939–1944) the same principle, stated above, which Pariser established for early syphilis (1942)

The presence of *Spirochaeta pallida* in breast milk, of great importance in wet-nursing practices was apparently demonstrated by Uhlenhuth and Mulzer ho infected rabbits from the milk of three seropositive women otherwise free of symptoms. Sch arts has, however failed after careful search t find *Spirochaeta pallida* as such in breast milk.

Of great importance to the carrier problem in syphilis and to the practical epidemiology of syphilis is the question of the infectiousness of vaginal secretions in syphilitic women. Pariser (1940–1941) has most recently and extensively reviewed the literature and discussed his own experimental results. He concludes that virulent *Spirochaeta pallida* are discharged by the syphilitic woman into the vagina in the presence of local early or "late (more than four years duration) infection as relapsing phenomenon. I the absence of such lesions they are discharged only through the menstrual blood of the early syphilitic, or from an abnormal appearing cervix *in which instances it is probable that lesions are present within the cervical os or uterus.* The physiologic secretions are not infectious. Pariser was unable t give the absolute end point of the period of infectiousness or the frequency of cervical relapse, but found that it occurred at least six and one-half years after the definite onset of the disease.

Viability of Spirochaeta Pallida.—The anaerobiosis of *Spirochaeta pallida* and its inability to resist drying have probably spared mankind the absolute universalization of the disease. The distinction between virulence, preservation of motility and *preservation of form of Spirochaeta pallida in secretions* and tissues outside the body must be insisted upon.

Infectivity of *Spirochaeta pallid* in refrigerated citrated blood can be demonstrated up to about the third day (seventy-two hours) (Turner and Diseker 1941) Fresh citrated blood heavily seeded with virulent *Spirochaeta pallida* may undergo spontaneous sterilization in seventy-two hours when kept at 4 to 6° C. Plasma (citrated) is spontaneously sterile in twenty-four hours (Kolmer and Rule (1942)) Ravitch and Chambers (1942) found human and rabbit plasma (frozen)—20° C. for forty-eight hours or longer is not infectious for normal rabbits but is infectious when the freezing period is only twenty-four hours. Bloch (1941) observed that the organism in rabbit blood survives for as long as seventy-two hours at 5° C. Turner Bauer and Kluth (1941) showed that freezing desiccation kills *Spirochaeta pallida*. Zinsser and Hopkins found that the organism in darkfield preparations at room temperature by daylight died out in approximately eleven and half hours, and that this is approximately its life in secretions contained in moist handkerchiefs. Mahoney in studies of delayed darkfield technic, found that motility may be observed up t ninety-six and one hundred twenty hours or even longer after collecting the specimens, and that entirely recognizable forms were observed in an icebox preparation thirteen

days after collection. Harrison reported motility as late as thirty-four and even forty four day after preparation of slide specimen, and that specimen containing motile organisms could be shipped repeatedly back and forth across the Atlantic. Lacey and Haythorne found the organism still motile in autopsy material refrigerated for forty-eight hours, and were able to preserve motility in sealed tubes for specimens of syphilitic rabbit testicle as long as fifty-eight days. Syphilitic autopsy material was infective twenty-six hours after death the chancre twenty-four hours after excision syphilitic rabbit testicle twenty-four hours, but not as long as fifty-four hours after excision. Rosahn (1933) infected rabbits as late as seven days after excision of the testicular syphiloma but in no case after fourteen days. The organism dies quickly at 2 degrees centigrade cannot live below −10 degrees centigrade dies in seven to ten minutes at 45 degrees centigrade and five minutes at 60 degrees centigrade (Klemmeyer- Bronfenbrenner and Noguchi) More recent work by Turner (1936) indicates that infectious material from rabbits after freezing in the case of both syphilis and yaws, produces infection as late as four months after freezing. More recently Turner extended this period to a year at −78 degrees centigrade.

Thermal Death Point of Spirochaeta Pallida.—Boak, Carpenter and Warren (1932) determined by in vitro studies that *Spirochaeta pallida* was immobilized at 39° C. (102.2° F.) for five hours 40° C. (104 F.) for three hours; 41 C. (105 8° F.) for two hours and 41.5° C. (106.5° F.) for one hour Bessemans (1938) concluded that local temperature of 42° C. (107.6° F.), sustained for one hour or of 40° C. (104 F.) sustained for two hours, or even slightly lower temperature sustained for many hours, sufficed to bring about the immediate or gradual death of *Spirochaeta pallida* in the primary testicular syphiloma of the rabbit and in the external lesions of primary and secondary syphilis of man. In contradistinction t these results, *Spirochaeta pallida* of the popliteal lymph nodes of the syphilitic rabbit hardly ever lose their virulence if treated in vivo by heat for similar time interval sometimes it is necessary to destroy these germs, to sustain temperature of more than 40° C (114.8° F.) Klauder (1939) determined that it required t least t minutes to kill the organism when heated at 140° F (48 9° C.) in vitro.

Resistance to Disinfectants and Drying.—Soap has been shown by Reasoner to have a powerful germicidal and solvent action on *Spirochaeta pallida* even superior to that of many widely advertised disinfectants 1 1000 phenol kills the organism in fifteen minutes, while 1:20 formaldehyde which will kill *Staphylococcus aureus* and *Bacillus coli* in a five-minute exposure will not kill *Spirochaeta pallida.* 1:500 formaldehyde however is effective The sulfonamides are without direct destructive effect on *Spirochaeta pallida* (Pariser) The drugs employed in the treatment of syphilis (arsphenamines bismuth) have been shown by Eagle s work to be much more spirillicidal in vitro than the studies of earlier investigators indicated.

It is generally agreed that drying under any circumstances is almost immediately destructive of *Spirochaeta pallida*

Epidemiologic Considerations.—In dealing with the syphilitic patient as a problem in infectious disease it becomes evident then that the critical issue is the disinfection of the tissues of the host rather than the fomites Moist material become the only possible source of transmission, and this does away with the necessity for disinfection or special cleansing of rooms or dry fomites. On the other hand dressings with moist discharges objects such as pipes cups and instruments which may be passed from person to person may be extremely dangerous. Gaston and Commandon found that *Spirochaeta pallida* lives for 30 minutes on glasses washed only in cool water Even antiseptics may fail to protect where the organism is shielded by a dense precipitate of protein Cleansing therefore becomes a necessary pred ecessor corollary nd in many cases the entire mechanism of prevention and soap and wat nd especially soap achieve unprecedented importance in prophylaxis Th adaptability of *Spirochaeta pallida* to the conditions of invasion and und t bed parasitic existence in man is such that infection takes place too ofte when lea t expected and in spite of what may seem to

be all reasonable precautions Unawareness is therefore the great danger in encountering syphilis, and increases every type of risk in both physician and patient. The peculiarities of the organism explain the genital transmission of the disease for only about the flexures and in and near the mucocutaneous orifices are the requisite combinations of moisture erosion of lesions liberating spirochetes, and quasi-anaerobic conditions combined Syphilis is therefore inevitably a disease of intimate contact, and moreover of intimate contacts rendered unguarded by emotion by inconspicuousness or concealment of infective lesions by painlessness, by ignorance. Kissing and sexual intercourse are therefore the overwhelmingly frequent sources of acquired infection with syphilis. It is well worth while in discussing syphilis with patients whose perspective is much distorted with reference to the moral problems of the disease to direct their attention to this aspect of the matter It is not a divine moral purpose or a satanic punitive ingenuity that connects syphilis with genital activities, but a mere biological accident no more significant in the last analysis than the fact that potatoes grow in sandy loam The comparative infrequency of infection among those whose professional duties as physicians, nurses and dentists, bring them constantly and intimately into contact with the disease is only relative and the ever present risk to which members of these professions are subjected should never for a moment be forgotten

PARASITE HOST RELATIONS

Symbiosis.—The outstanding fact in the general immunological background of syphilis and one which Warthin in his teaching never tired of emphasizing is the extraordinary adaptation of the *Spirochaeta pallida* to its life in man. An organism which in nature affects no other species and which in the vast majority of cases is able to maintain its foothold in tissue literally through decades of almost symptomless infectivity meeting a wide range of growth conditions and therapeutic opposition with an almost unbelievable ability to survive every test, is easily one of the sovereign instances of parasitic adaptation in the entire field of disease. Experimental study has only served to expand our conception of the perfection of this symbiosis

The Syphilitic Carrier —Basing his position upon the now inescapable evidence of lifelong symptomless infection in the rabbit and mouse with complete absence of tissue reaction against the invading organism Kolle has proposed the theory that there exists in man not only the familiar clinical picture engendered by reaction against the organism but a state of complete carrier immunity or anergy against the infection Thus it may be conceived that there are human beings who have become carriers of syphilis without any outward sign of reaction either at the point of invasion or elsewhere in the body and that these persons live out their lives as carriers almost if not quite unaffected by the presence of the parasitic organism and even conceivably transmitting the disease or sustaining superinfection with a new strain practically without any form of tissue response That such infection as, for instance, of the lymphatic system of the rabbit, is well known to occur does not, however justify too ready transfer of principles established by animal observation to the case at hand.

The interplay between host and organism in syphilis is evidently an extremely complex affair It is extremely difficult to study it in man because it is rarely possible to control more than two factors, namely the strain of organism and the duration of infection, or those element,

in any given group of comparable cases. The commonest example, infection of husband and wife with the same organism, is weakened by the adventitious factors of sex, by passage through an intermediate host, usually the husband, before reaching the wife, and by variations in the behavior of infection dependent on the site of inoculation. For example, in the case of two brothers infected by the same woman at the same time, the two infections ran totally different course. One brother developed conspicuous chancre and definite secondary manifestations within the usual incubation period. The other developed three penile sores two weeks later than his brother. The lesions were cauterized, no secondary eruption developed and the systemic infection was discovered only when Wassermann test was made following the development of the brother secondary eruption. Both brothers were placed on the same treatment, the condition of the first one clearing up rapidly and apparently permanently: the other who had had no secondary eruption and whose immunity mechanism was presumably modified by that fact, nine months later presented the fulminating precocious disseminat recurrence of an inadequately treated early infection. In another instance under our observation, family group of four persons studied for five years and all infected with the same strain of organism, it was found that the father and one son presented highly resistant neurosyphilitic manifestations, and the mother and the other son had quiescent, benign but Wassermann-resistant infections. The familial resemblances in this group, so far as appearances go, support the apparent resemblances in the soil reaction t the seed, the two neurosyphilitic patients resembling each other in appearance. On the other hand, Livingood and Beerman (1941) record the similarity in course and outcome of single strain of syphilitic infection, transmitted by blood transfusion in two brothers, who ran resistant course despite the employment of two differing but theoretically adequate and effective modes of treatment

It must be apparent, therefore that the course of a syphilitic infection in any given case is controlled by numerous complex interacting factors whose proportionate relationships and significance are as yet only partly understood

Resistance and Susceptibility—Morgan (1941) following Chesney s suggestion diagrammed the possible clinical course of syphilis, allowing 33 per cent to 35 per cent asymptomatic infection with 25 per cent to 35 per cent spontaneous "cure within the first twenty years of infection. The first influence which may affect the course of a syphilitic infection in the individual is presumably an intrinsic resistance or susceptibility to inoculation on the part of the host. On this point, while clinical evidence furnishes some presumption, it must be conceded that no positive statements are possible

Reported illustration exists of the exposure of individuals t virulent infection without subsequent inoculation, at least so far as such inoculation can be detected clinically On the other hand, it is now ell know that symptomless onset nd symptomless course ith unquestionable infection of the lymphatic system direct, even through an unabraded mucosal surface is possible in the rabbit and is, of course, by no means inconceivable for man. Brandt, in an extended study of syphilis in prostitutes, has the impression that an actual resistance t infection may exist and that omen ho do not acquire the disease early in their career subsequently escape it entirely Legram and Schulmann have published examples of what ppears t be outright, if only temporary immunity against virulent risk of infection. Metchnikoff and Roux reversed the logical process by showing that susceptibility mong the pes increases as one ascends the evolutionary scale and decreases in the lower orders.

The influence of resistance of the host on the actual course of a syphilitic infection after inoculation is likewise made difficult to define because it is unavoidably entangled with the problem of strain, of elective localization of the influence of the rate of reproduction of the organism at the time of inoculation of till unknown factors affecting its distribution through the body of the site of inoculation, as Brown and Pearce have demonstrated in the rabbit, and other influences a yet undetermined

Reference ha already been made t relative and variable resistance within susceptible group, as in the case of rabbits, here young animals undoubtedly offer the highest proportion

of "takes." Seasonal and dietetic factors have been recognized by Brown and Pearce and by Greenbaum, by Sulzberger and others, the summer months and green fodder apparently protecting, to some extent, against inoculation. Sunlight has also been shown by Brown and Pearce to influence the course of the disease in laboratory animals. Pearce and Van Allen found that in partially thyroidectomized rabbits, syphilitic infection tended to run milder course than in totally thyroidectomized animals. Pearce has also shown that rabbit inoculated in the testicle with syphilis and at the same time in the skin with vaccinia develop severe syphilis, but rabbits immunized t vaccinia as well as those inoculated intratesticularly with both vaccinia and syphilis develop milder disease.

So far as man is concerned the influence of race sex and pregnancy will subsequently be more fully discussed. Notwithstanding some suggestions to the contrary there is as yet no convincing evidence that in man, inoculation around the head or face or on the mucosa of the upper respiratory tract or inoculation directly into the blood stream by transfusion significantly modifies the general course and manifestations of the disease. (See however Pian and Framer "Transfusion Syphilis" 1040)

Vascular and Lymphatic Localization of Spirochaeta Pallida.—One of the most obvious localizations of the organism has probably escaped more emphasis because of its universality—namely that to the vascular system. While of course undoubtedly influenced by the mode of distribution of the organism through the blood stream the tremendous importance of syphilis of the blood vessels in every phase of the disease as a whole points as strongly as any single piece of clinical evidence toward a distinct vasculotropism Olsen (1938) summarizing Warthin s, Starry s and his own studies of the morphology of *Spirochaeta pallida* described a distinctive "small form in addition to typical spirochetes, granular ringed and filamented forms, in late syphilis of the aorta.

The complications centering about vasculitis and perivasculitis from aorta to capillaries are legion, and have even been invoked by critical students of the pathology of the disease such as Brown, as quite sufficient explanation without reference t allergic phenomena for most of the late manifestations of the disease. In ordinary clinical experience one finds certain persons predisposed toward certain types of involvement in truly wholesale fashion, as in the patient in Fig. 801 whose bones seemed to be veritable target for his spirochetal invader or as in the patient in Fig 508, who developed a remarkable series of Charcot arthropathies with his tabetic neurosyphilis. While superficially at least these may be interpreted as differences due t susceptibility of the host structure there are too many other factors, such as accidents in initial distribution and peculiarities of the strain of organism involved, to permit of definite decision. The almost uniform occurrence of interstitial keratitis as complication of heredosyphilis may be an example of predisposition of tissue or t may be evidence of the effect of the mode of inoculation on the course of the disease

The tissues of the lymphatic system probably stand next to those of the vascular system in their susceptibility to inoculation and their activity as carriers of the infection In fact, the term lymphatic reservoir" is a tribute to this predisposition Moore (1930) points out the perfection of symbiotic relation between host and organism in the lymphatic system In the rabbit, the organisms persist there for the life of the animal but in man, according to Moore they tend to disappear The high virulence of lymph node material in which no spirochetes are recognizable by darkfield (Bessemans) should be remembered The influence of latency in changing the propagative and pathogenic properties of the *Spirochaeta pallida* has been touched upon by Engman and Eberson but has not elsewhere as yet received the study which its very great importance demands.

In studying the distribution of infectious recurrences as they occur in *relapsing early syphilis*, Besancon, Seboch and Stokes were impressed with the uniformity and high proportion of genital involvement in this particular type of lesion. Genital relapse so strikingly outnumbers all other types of relapsing cutaneous and mucosal lesions as t seem almost t constitute evidence of a distinct elective localization, if not tropism.

Infection through a Break or Abrasion.—Curiously enough, tradition has proved to be in error in one of its seemingly best established tenets with reference to the influence of trauma on inoculation with syphilis. The common belief that an abrasion or break in skin or mucous membrane is essential to the penetration of the *Spirochaeta pallida* into the tissues has been negated now by so much experimental evidence that it may be regarded as definitely disproved.

Neisser early pointed out that rupture of continuity if it existed, need do no more than give entrance t lymphatic radicle and need not of necessity involve blood vessel. The subsequent experiments of Brown and Pearce and Mahoney and Bryant (1934) have shown that inoculation even through the highly resistant vaginal mucosa of the rabbit takes place without any trauma whatever and that while no reaction may ppear at the site of entry involvement of the lymphatic system rapidly follows. In man, the appearance of the chancre at the site of inoculation is, of course, the expected sequel of the entry of the organism but there is much reason to suppose that the primary reaction may be absent and inoculation show its first signs, not at the point of traumatic entry but in the adjacent lymphatics (bubon d emblée) Infection of old and healing wounds has been reported in man, and a probable case of such an occurrence is shown in the case of a herniotomy wound in Fig. 290. Chesney showed the granulating wound in the rabbit t be specially reactive to inoculation.

Needle-prick (Surgical) Inoculation. Syphilis d'Emblée.—Traumatic inoculation by injuries incurred in the course of surgical operations such as needle pricks, is well established A distinctive and unfortunate feature particularly of the needle-prick inoculation is the asymptomatic character of the onset. The general group of asymptomatic onsets is spoken of as *syphilis d'emblée* a category which has been steadily reduced by critical examination of patients and records to discover an occult, inaccessible or trivial primary lesion. The onset of syphilis in the intra-urethral chancre is a particularly frequently overlooked lesion in supposed asymptomatic onset. Burbi differs from us in believing that transfusion syphilis runs a distinctive course.

Trauma in Syphilis. The Locus Minoris Resistentiae.—A broad definition of trauma to include not only injury but overstrain, would place traumatic influences among the principal factors in the localization and course of many aspects of syphilis. There is unfortunately an unexpected quality about the effect of trauma which may make it appear of small significance in an individual case Unquestionably the chief significance of trauma appears in the later periods of the disease

Cazenave is credited by Klauder bo has been the chief American student of the clinical side of this problem, with being the first t recognize traumatic influence in provoking syphilitic manifestations. Ricord mentions it and irritation as trauma in the form of tobacco, dirt and friction has long been regarded as cause of infectious recurrences in the mouth and around the genitalia. Development of lat syphilis in tattoo marks (fine example by Keidel) and palmar syphilis of laborers are recognized. T masz ky *cauterisatio provocatoria*, the production of gummas on the skins of syphilitic patients by caustic past proposed for diagnosis, remains unconfirmed at least with regard to the presence of *Spirochaeta pallida*, by Greenbaum and Madden study (1932) Experimentally the resistance of rabbits against reinfection with homologous strains can be broken down by injury as demonstrated by Chesney and Kemp Even with the homologous strain, against hich high degree of resistance is t he expected it was possible

I secure "takes" in 7 out of 16 rabbits as demonstrated by lymph node transfer though only one animal developed a chancre

Gumma in Surgical Scars.—Development of gummatous manifestations in the scars *of healing* wounds of surgical operations is known especially in operations involving the nasal septum and pharynx in heredosyphilis Goeckerman s general study of this problem as a factor in surgical recovery indicates that the large majority of surgical patients with syphilis may be operated upon with impunity from the standpoint of wound healing Scheffey has *recently confirmed* these observations and Wiltrakis and associates (1941) found the general surgical risks and mortality of syphilitic and nonsyphilitic groups very similar Nonetheless, it is evident that incision or trauma inflicted upon tissue that has already undergone gummatous change is a very different matter from operation on the normal tissues of a syphilitic patient The reaction of gummas that have been traumatized or operated on is immediate and disconcerting, a rapid and destructive extension and prolongation of the process being the almost invariable result. Numerous examples of gummatous changes in war wounds were recorded during World War I

Other Traumatic Complications.—Gumma of the testis occurs following trauma and delay or nonunion of fractures is also known to be at times due to gummatous changes. Klauder describes cases in which the Wassermann reaction became positive after trauma, although repeatedly negative before Landouzy s case of an army officer who, after twenty five years of latent syphilis, developed an osteitis following a fall from his horse is typical of a considerable group of reported observations. Tumpeer quotes Lacapere and Laurent, who observed fourteen gummas of the forehead in forty Moslems, due to trauma from the rubbing of the frontal bone while kneeling Moslem fashion, with the forehead against the stone floor of the mosque Injury to the head has long been thought to be the starting point of clinical manifestations of paresis in certain patients. After a critical examination of this question, Klauder and Solomon endorse Calvi s summary of the medicolegal status of the relation of trauma to dementia paralytica. This states in effect that trauma, while not an exclusive may be an occasional cause of dementia paralytica and that three types of cases may be distinguished in the first *of which the period of latency* and recovery *after the injury is too long* to permit a causative interpretation in the second symptoms of dementia appear immediately after the trauma and the injury itself is to be regarded as an aggravating but not a causative event and third a type in which the interval between dementia and injury is neither too short nor too long and previous mental health can be completely established Nonne (1940) believes that trauma as a precipitating cause of central nervous system syphilis, can be overemphasized as shown by the experience in severe head and spinal cord injury in syphilitics in the First World War Numerous case examples will appear in the material of subsequent chapters in this text and the wide variety of traumatic influence which, as Gougerot and Clara point out, may follow every type of injury mild or severe sudden or prolonged single or repeated will be illustrated.

Industrial Trauma and Syphilis.—An expanding interest in syphilis in industry brings out an increasing case literature on the importance of trauma in the syphilitic employee (Stokes Beerman and Ingraham 1938) Eliet,

under the prof... ...l p... ...d anselme la...d ...n in 1936 a ...ummary which ...e con tantly ...ju...ted by person concerned ...t... ...la... with the in...ence of trauma in syphil... (Hees...n 1936) His cl... ...ficat...on ...f it effect includ... (1) a ...ngle an...l ...dent trauma (2) a ...n...d mild traum... and (3 mild trauma repe...tedly applied ...e all ...f these th... in...l... trial ...ly ...man ...ould be con...tantly ...n h... gu...rd in ev...lu...t...g the potent...al ...gn...ficance ...f ...p...l ...in any injury ...e...e h... company Th... imp...rtance of complete ...valuat...on ...f th... syphilitic patient from the ...tand...p...nt ...f a...mpt...matic neur... syph...l... must be particularly ...tressed in th... connect...on for injury ...ee ...w...ll negat...e serol...g...c test and a h...t...ry ...f treatment in which ...e ...l...t...n of th... ...tatu... of the nerv...u... system ha... been overl...oked can furn...h ...s...me ...f the m...st ...tartl...ng and seriou... ...xampl... ...f th... acti...t...n ...f nerv... ...ystem in...l...ment by trauma (Leschia 1930 and Bethel ...m...r 1933 It h... ...l...l be p...inted out al... that the que...tion ...f infecti...u...ne...s ...t ...ent...ngled with the trauma ...ue and that *Sp...ch...eta pall...d...* may appe...r in early syph...l...t...in le...i...n induced by vesicant and ...ther traum...ti...ng agent ...Frankl...l...9... N... ...ser ...ee Kl...uder and S...l...m...n 1934) ...f cour...e observed it in th... skin ...f ...ph...l...tic patient ...in wh...m no trauma wa... present Some of the practical a...pect... ...f th... problem a... it affect... indu...try have been ...umm...rized by May (1934)

THE INTERACTION OF ORGANISM AND HOST
PATHOLOGIC PHYSIOLOGY OF SYPHILIS

The Local and Systemic Reaction Phases Th... fart...r ...l...th cl...nical an...l ...xperimental ...phil...l...gy progre...s th... clearer it becomes that th... reaction of the body to the *Spiroch...et... pall...da* inv...l...e... two phases both ...f great importance and to some ext...nt ...nt...r...w...en These are the local reaction t... a ...pirochetal focu... wheth...r it be ...hancre secondary papul... or lat... gumma, and the general ...mmun...l...gical reaction ...f th... ...rgani...m a... a whol... Thi... furni...hes a convenient ...ul...l...i...on f...r the con...ider...t...on ...f the pathologic phys...ol...gy and h... in additi...n an important and perhaps somewhat unex...pected bearing on the ...linical problem In order to ma...ntain a convenient cla...sification ...f phenomena and to mak... the interrelation clearer the experimental and laborat...ry a...pect... ...f the ...isease w...ll be con...idered in a...lvance ...f the cl...nical applicati...n

We have alrea...ly mad... it clear that trauma and abrasi...n, while th... favor are not essential t... th... inva...i...n of the body by the *Spirochaeta pallida* Neither i... it nece...sary th...t any vi...ble f...rm ...f reaction ...ccur at the point of entry to mark t...e to serve a... a l...cal f...cu... f...r the b...dy... first battle aga...n...t the disease While ...yphil... without chancre i... known to ...ccur both experi...mentally and in man ...yphil... with chancre i... the u...ual rule at lea...t in initial infections, and the chancre or primary lesion i... the prot...type of million... of local reaction... occurring through...ut the body ...ubsequently in the course of a syphilitic infection These l...cal reaction... may be modified by allergic phe...nomena a... in the case ...f gumma, and may lead t... train ...of ...ymptom... depend...ent upon locali...zati...n a... in the case of vascular involvement but the funda...mental pathology of th... original lesion run... so true to form throughout the course of the disease that it i... unnecessary to describe ...ver and over in indi...vidual detail the reacti...n... ...ccurring in separate organ... and different tissues during the vari...ou... phases of the ...isease The first ...t...p after penetration is an invasion of the peri...vascular lymphatics by the *Spirochaeta pallida*, followed

by a vascular reaction which assumes the form of endothelial swelling with proliferation and development of an obliterative endarteritis. This is accompanied by perivascular infiltration with lymphocytes the appearance of plasma cells, and finally fibroblastic proliferation and healing Immediately following inva ion and during the phase of vascular and perivascular reaction, the spirochetes increase rapidly in numbers Penetration of the surrounding lymphatic channels and the escape of the rapidly reproducing invaders into the blood stream where they continue to reproduce, go on to an increasing extent. It was pointed out by Kolmer in 1920 and experimentally confirmed recently by Brandt that material from rapidly growing primary lesions gives rise to more rapidly growing chancres than those which develop when infective material is taken from a slow-growing lesion This would certainly argue that there is a species of dynamic drive involved in the reproductive rate of the *Spirochaeta pallida* and that a rapidly reproducing strain such as would be obtained from an infection acquired from early acute lesions may be capable of rapidly flooding the system as well as the local focus with organisms. At the height of its development the local focus, whether a chancre on the genitalia or a colony of spirochetes in the liver becomes a contributor to the systemic infection and to the local area of lymphatic infection to a degree proportional to its size and the reproductive activity of the parasites. Then a change takes place as the histologic signs of healing begin to appear Fragmentation of the spirochetes can be recognized, the number and viability of the organisms decline granular change in the spirochetes appears followed presumably by phagocytosis of the granules by the lymphocytes attracted to the scene of reaction. The focal infection begins to subside.

Significance of Local Healing.—If the reaction which inhibits and destroys the organisms in each local focus throughout the body in the period of secondary eruption for example could be persuaded completely to perform its duty immediate spontaneous cure would result in all patients and the clinical syphilologist would become extinct. Unfortunately the successive inoculations of adjacent and distant tissues produced by the multiplying penetrating and escaping spirochetes prolongs the disease almost indefinitely while the fact that structural healing does not necessarily mean sterilization, prepares the way for a certain percentage of local relapses. It cannot be too strongly stated that even though the activity of the surviving organisms at the site of a healing reaction may be temporarily suspended sooner or later in a considerable proportion of the foci, some degree of relapse occurs. The defensive mechanism which has developed loses its effect, the tissue immunity wears off and the reproduction of virulent organisms may be resumed followed by reinoculation of the local lymphatic area or even of the blood stream A fresh reaction in the newly infected tissues then begins and syphilis once more resumes its cycle of infection, reproduction, reaction, suppression and relapse.

Healing in a Syphilitic Lesion Is Therefore Never a Proof of Cure.—In fact, it is possible, by a selection of therapeutic methods to induce the healing of a syphilitic lesion without materially affecting its spirochetal content. Müller Kitchevatz, Pasini, Wechselmann and Arnheim E. Hoffmann Sandmann have confirmed and even proposed for diagnosis, the finding of *Spirochaeta pallida* in chancre scars.

Brown and Pearce, working, for example, with compound in the series prepared by Jacobs and Heidelberger arsenophenylglycyl-dichloro-amino-phenol, found that this drug suppresses the tissue reaction and produces immediate healing of the syphilitic chancre in the rabbit but

[illegible]

Fundamental Nature of Reaction. [illegible]

Relation of the Local Lesion or Chancre to Immunity and Defense.—The local lesion [illegible] many battles [illegible] struggle between [illegible] battle [illegible] character [illegible] integrity [illegible] reaction [illegible] local immunity reaction [illegible] to the reaction of the tissue and [illegible] reaction [illegible] or protection [illegible] through extension [illegible] ment and reaction [illegible] local immunity [illegible] it is also conceivable that the local lesion, especially if it be extensive, may not be important [illegible] but [illegible] a general mechanism of defense which [illegible] protect [illegible] even though they may not have been up to that time in the [illegible] history of the individual disease invaded by *Spirochaeta pallida* itself.

Thus the chancre in the rabbit, for example, [illegible] effect on the progress of the infection [illegible] in the text. One of [illegible] already mentioned [illegible] observed by Brown and Pearce [illegible] effect is that rabbit be amputated, immediate generalization of the infection [illegible] result. If the local tissue reaction be suppressed therapy [illegible] the infection, freed of the restraining influence exerted by the local reaction, disseminates through out the body in exactly the same [illegible] as if the chancre were [illegible] becomes apparent that the almost infinite number of local tissue reactions occurring in all parts of the infected animal or human body are the essential contributors to whatever general defense [illegible] the patient against such a disease as syphilis. T. Warthin particularly [illegible] the distinction of emphasizing to the pathologist and clinician the meaning of this local defense for the mechanism of latency to be presently mentioned. That the chancre reaction [illegible] in the initial infection

of man, has relatively unimportant controlling effect upon the fate of the syphilitic infection in his body as a whole is attributable, as Brown has pointed out, to the insignificant size of the lesion as compared with the mass of the whole body In the rabbit the scrotal chancre is the equivalent perhaps of several hundred human chancres in defense-producing capacity and for that reason it exerts much greater influence upon the course of the disease in the experimental animal than does the primary reaction in man. In fact, the reaction of the multiple foci in the human skin in the course of the secondary eruption is probably much more nearly comparable with that which occurs in the scrotal chancre of the rabbit.

As will presently appear then there is much evidence to support the belief that, so far as the individual himself is concerned multiple focal reactions in his skin in other words an extensive secondary eruption, permanently and favorably influences the subsequent course of his infection It must be emphasized here and repeatedly hereafter however that this form of individual protection has its weaknesses as well as its advantages and particularly from the standpoint of the public health in our present knowledge of the disease and of treatment must be to a large extent disregarded

Systemic Reactions.—Our knowledge of systemic or general reaction to a syphilitic infection in the experimental animal has not progressed so far as has our comprehension of the local reactive mechanism. Both clinical and experimental knowledge tends to support the importance of the lymphatic defense mechanism and its histopathologic background has been studied by Zurhelle Bergel Engman and Eberson, and most recently in man by Saleeby and Greenbaum and by Michelson The reticulo-endothelial system has been presumed to bear an important part in this mechanism but the suggestion of this influence comes rather by way of therapeutics than direct observation. The induction of reticulo-endothelial block by trypan blue and *Eisenzucker* has the effect of suspending the action particularly of arsenicals in the treatment of syphilis. The precise significance of this connection for the place of the reticulo-endothelial system in the spontaneous defense mechanism is not as yet clearly understood but there is little doubt the system plays an important part at times.

Organs and Structures Involved in Defense Reaction.—The importance of certain groups of tissues in defense against syphilis becomes more apparent when particular organs are considered. Brown and Pearce in particular have shown that the testis, the bones, the skin and the eye (Chesney differs) successively take up the protection of the body as whole and provide by their local reaction mechanism the source of much of the general physiologic defense. Observations of this sort substantiate the clinical tradition that human patients who have had extensive syphilis of the skin, bones and parenchymatous viscera such as the liver and spleen, usually escape the most serious forms of damage in the vascular and nervous systems, whose reactivity to infection is comparatively low and whose intrinsic defense is therefore weak.

Antibodies Agglutinins and Lysins.—The hope of finding a serum or vaccine cure for syphilis combined with the antigen antibody series in the mechanism of the Wassermann reaction has inspired a most thoroughgoing search on the part of many investigators both of man and animals for any signs of a general serological immunity reaction to the disease which might be utilized in treatment In general it may be said that every effort thus far made, based on the investigation of the properties of the blood serum of man and animals tested against virulent spirochetes from animal and human syphilitic lesions and against cultivated *Spirochaeta pallida*, has ended in failure In other words, the inference is that such general defense as exists against syphilis, resides in the tissues and in the cellular mechanism and is not present or distributed as a circulating substance or property

The ... literature on this subject may be followed in the summaries of Maher (Jadassohn Handbuch) and Chesney and Harrison (1931) ... Kast and Lynch (1941) and Kolmer (1942) bring the literature of the subject up to date. While it has been shown that agglutinins and lysins for *Spirochaeta pallida* are formed, the amount ... of ... effect on the disease is uncertain. ... enhance reducing properties on the blood serum of latency ... and ... Lowell ... have found certain ... properties for Kahn serum have failed ... The most interesting current discussion concerns the relation between the recognized agglutinins of *Spirochaeta pallida* and the Wassermann reagin. Kolmer and his group ... they have shown them to be fundamentally different, and Beck (1939) likewise ... and ... (1940) believe that ... seem to be identical, and to be, in fact, true spirochetal ... Turner (1939) showed experimentally that in the course of syphilitic infection specific humoral ... can be demonstrated by an ... "protection test." ... (1940) concluded that ... of *Spirochaeta pallida* in tissue produce ... serum in ... The ... attempt to extract ... *Spirochaeta pallida* ... (Hillerman, 1941 and Stratton, 1941) ... Stratton ... protective ... susceptibility in experimental animals. Becker (1939) ... serum, concludes that it renders ... more resistant to experimental ... Kahn ... theory ... the conclusion is ... that ... rather ... form of natural or stimulated immune ... reaction must be relied upon to control the individual infection.

Nonspecific Defense.—The systemic physiologic defense against syphilis has an element of nonspecificity probably imported into it by the multiple factors now so many times mentioned which must be borne in mind in interpreting the behavior of the disease under treatment. Not all of the effect of medication is on the spirochete itself and not all of the systemic effect of treatment is specific for syphilis. The action of foreign protein, of course, at once occurs to one as a fundamental example. The effect, however, may be observed even in medicaments whose action is supposed to be specific, such as that of the arsphenamine. Practically every drug used in the treatment of syphilis is capable of arousing a certain nonspecific and fixed element of defense which, while it acts on the syphilitic infection most markedly to be sure, is also capable of acting on tuberculosis and blastomycosis, for example. This nonspecific factor, repeatedly discussed in connection with treatment in subsequent chapters, is an important general ally in behalf of the patient.
Immunity relations and defense are revealed in reinfection, superinfection and cure in animals. It will serve the double purpose of clearly differentiating between what is known of syphilis in the animal and what is known of the same disease in man, if at this point we summarize the critical problems and conclusions in regard to these vital questions as they have been illuminated by animal experiment. The critical experimental question and one with wide sweep of practical significance, if the findings can be transferred to man, relates to the persistence of the *Spirochaeta pallida* as a necessary condition on immunity to reinfection. A positive or negative answer to this question would establish the position of reinfection as an absolute criterion of the complete extinction of every last spirochete in the animal body or of the establishment of an immunity or resistance to the disease intrinsic to the body itself and not dependent upon the continued presence of the organism. If it can be shown that every last spirochete can be extinguished and the animal yet remain for an indefinite or a limited period of time refractory to reinfection, reinfection ceases to be the proof of cure which it has been considered to be in the past. The gateway of hope for the complete extinction of the disease with more or less lasting immunity to it begins to open, provided the conclusions are transferable to man.

On this extremely important question, two distinct schools of thought exist. Neisser Kolle Frei, and Prigge have contended that resistance to reinfection is dependent on the persistence of the original infection. In other words, an animal which cannot be reinoculated is still infected. Chesney and Kemp Voegtlin and Dyer Uhlenhuth and Grossmann, Manteufel and Richter Worms, and Brown and Pearce on the other hand, have maintained that an actual resistance to reinfection develops independently of the mere persistence of spirochetes and that an animal may be apparently immune to second infection while coincidentally free from the first infection In the process of development of these opposing concepts, a variety of important facts have come to light as follows (1) Shortly after development of a primary lesion, a second primary lesion cannot be produced by reinoculation. This observation is of course familiar in man and is designated in the original Neisserian conception of anergy or resistance and is now more frequently spoken of as chancre immunity (2) this chancre immunity is dependent on a reaction of the tissues and not on the mere presence of the organism. (3) Inoculation in certain tissues (for example, the cornea) does not protect against inoculation in other sites (for example, the testis) but certain tissue inoculations have greater general protective value than others. Moreover (Chesney Wood and Kemp 1929) the tissues of the eye in the rabbit do not share to the extent that other body tissues do, in the immunity state induced by syphilitic infection (4) An animal may harbor a syphilitic infection without reacting to it (Manteufel and Richter for the rabbit and Kolle and Schlossberger for the mouse) (5) In rabbits made carriers of infection by intravenous inoculation, the lymph nodes are infected the rabbit, however may be reinoculated with the same strain of organism while carrying the original infection in the lymph nodes and may from the second inoculation, develop typical syphilomas of the testicle (scrotal chancres) (6) Reinoculation of the rabbit on the site of a previous testicular chancre by a homologous strain of *Spirochaeta pallida* may take place in a proportion of instances, decreasing as the age of the infection increases. A larger proportion can be infected with a heterologous than with a homologous strain late in the disease (more than ninety days after infection) (7) Nonappearance of clinical lesions in animals after reinoculation is not a proof of failure to reinfect. (8) Chancre immunity the resistance to the development of a new chancre on reinoculation, is perhaps similar in kind to the slowly developed later absolute immunity to reinfection, but is less in degree, so that with only chancre immunity the animal may be reinfected, as subsequently proved by inoculations made post mortem from its lymph nodes and viscera. (9) The development of the complete or highest degree of immunity to reinfection varies in time with different individual animals and may be late or early depending on their constitution. There are intermediate cases in which the reinoculated organisms may penetrate only so far as the adjacent lymph nodes, where the infection may then be suppressed, or they may remain sequestered at the site of the second inoculation. (10) Superinfection, that is, the engrafting of a second infection upon a first one still present in the body may take place in rabbits after subcurative doses of the arsphenamines. The original infection thus remains latent and the lesions of the superinfection may so precisely resemble those of the original infection that they cannot be distinguished from each other without knowledge of the chronological and localization factors (Brown and Pearce)

It would appear then that the complete suppression of a syphilitic infection in the rabbit by treatment can be accomplished, but that there may persist after this infection (for the views of the Chesney and Brown and Pearce group of investigators seem to be gradually getting the upper hand) an immunity to reinfection which makes it impossible to use reinfectibility as a test of the cure of the original infection. It would appear moreover and this is a matter of vital importance in human syphilis, that subcurative treatment may instead of extinguishing an animal infection, merely reduce it to latency and that the animal may then be superinfected and develop new lesions while the original infection reduced to latency by treatment, still persists in the tissues Reinfection, even in cured animals, can only take place in those cases in which the chancre immunity and subsequent resistance developed are imperfect or of short duration. This use of the term "reinfection" must, of course be sharply differentiated from superinfection.

Allergy Gumma, and the Mechanism of Malignant Syphilis.—Just as the term *anergy* means a refusal of the tissues to react against the *Spirochaeta*

pallida, the term "*Umstimmung*" (Neisser) roughly translated by "allergy" implies a hyperreactivity on the part of the tissues to a local focus of spirochetes. We have seen that the conventional mechanism of defense against the *Spirochaeta pallida* is essentially a chronic inflammatory one and that the organisms disappear from the local focus, resistance being established coincidentally with the process of healing fibrosis. This type of reaction is fundamentally characteristic of the early, the latent and many of the changes of the late aspects of the disease. In a certain proportion of subjects, however, an allergic or hypersensitive state supervenes upon infection usually late in the disease but occasionally and especially under the influence of treatment comparatively early in the infection. The allergy or hypersensitiveness so far as it can be at present interpreted seems in the animal at least to be a function of the individual host rather than of the strain of organism. It may be predisposed to by intercurrent influences. It is probably inadvisable to speak of allergy in this connection as a form of defense though there can be no doubt of its tremendous and in fact explosive efficiency in destroying the small numbers of organisms which arouse it at the local site. Yet the histopathologic architecture of gumma as this late allergic local type of reaction is called has much in common with the more chronic forms of earlier healing reaction as in lymph nodes for example (Michelson). Gumma or better gummatous infiltration is the characteristic reaction of the late syphilid in structures such as skin, bone and other organ groups involved in the systemic defense mechanism already described. As a matter of fact, the essential differences between the early and the late gummatous inflammatory reaction are simply three. Gumma, in contradistinction to early syphilitic lesions contains so few spirochetes that their presence as a rule can be recognized only by animal inoculation. Secondly proliferative changes, necrosis and giant cells form a much more conspicuous part of the gummatous infiltration than of the other type of reaction. Thirdly from the clinical side gummatous infiltration is far more destructive because of its penchant for necrosis than are the local focal reactions in early syphilis.

The vascular changes are essentially the same both early and late and tend to differ only in degree. It must be conceded that able investigators have recently considered it unnecessary to invoke an extrinsic allergic factor to explain the peculiarities of gummatous infiltration. They feel the changes can be sufficiently explained on the ground of chronic vascular degeneration which have so reduced the viability of the tissues that a small number of organisms can produce marked destructive effect. Recently Warthin and Wile in reporting a unique case of fulminating destructive early syphilis, were able to establish through their pathologic studies that the classical picture of high grade malignant syphilis, in this case at least, was produced by thrombosis and obliteration of the medium-sized vessels forming the apex of the vascular cone in the skin. It appears, therefore, so far as this case may be used as a general example that a vascular cause may be invoked as an explanation of a good deal of what has passed as gummatous change of destructive character in both early and late syphilis.

Moore following Chesney maintains that the symptomless nonreactive carrier or latent state may be regarded as the anergic "response" to *Sp. pallida*, while the gummatous reaction type is the allergic, and that twenty-five per cent each of clinical syphilitic infections tend toward these types, with the remainder fluctuating between. None of these conceptions harmonizes particularly with that usage of anergy and allergy in tuberculosis, in which the proliferative gumma-like sarcoidosis is thought of as anergic tuberculosis — a tuberculosis without immune reaction, the tubercle being the allergic or immune reaction.

In connection with the discussion of gumma, it is wise to point out that the older clinical concept of gumma as the sole characteristic lesion of tertiary

syphilis need careful reinterpretation Gumma is not necessarily a massive or tumor like affair but may take the form of diffuse or miliary lesions in which fibrosis supervenes with relative rapidity thus avoiding the huge destructive breakdowns which are familiar in the large tumor like lesions Thus a gummatous infiltration of the skin may have the delicacy of parchment, may never ulcerate and may give rise to only the faintest signs of atrophy instead of the extensive and conspicuous scarring which conform more closely to the older conceptions. A gumma may vary in size from a microscopical lesion in the wall of a cerebral artery to a tumor the size of a grapefruit in the body of the liver but the fundamental pathologic mechanism underlying both lesions is identical

Specific Allergy and Cutaneous Tests in Syphilis.—The practical disappearance of luetin and its modifications from clinical diagnostic practice seems to justify simply a reference to the discussion in the second edition of this work, of the experimental background and status of the various spirochete containing suspensions tissue emulsions and so forth which have been tried for the clinical diagnosis of syphilis. Because of their nonspecificity uncontrolled or uncontrollable factors in their composition and a rather large margin of error as well as limitations in usefulness in the late stages of syphilis, preparations of the "luetin" type have been withdrawn from the market. The light thrown on the immunity mechanism so far as *Umstimmung* is concerned, is essentially that of indicating that iodide is capable of inducing in the body a physical-chemical state resembling the "allergic" state of late syphilis. So far as its cutaneous manifestations go this state can be to some extent imitated by breaking down any protein in the body even to the patient's own skin It seems therefore not impossible that the tremendous lysis of spirochetal protein which takes place under the action of the local defense mechanism early in syphilis may in a proportion of cases, prepare the way for the destructive allergic manifestations of late syphilis. It is also possible that lysis of the patient's own tissues at various times in the disease may furnish the necessary background. Such an explanation unconfirmed though it is, assists in the comprehension of the effects of spirochete-destroying treatment insufficiently followed through, in bringing on the dangerous early "allergy" and precocious tertiarism seen in the inadequately treated patients of the arsphenamine era

PRACTICAL APPLICATION OF PATHOLOGIC PHYSIOLOGY AND IMMUNITY CONCEPTS TO SYPHILIS IN MAN

The need for the systematic use of and constant reference to the foregoing conceptions of the pathologic physiology of syphilis in clinical diagnosis and treatment, is well illustrated by the decade lag almost universal up to 1917 between the lessons taught by the laboratory and the practice of diagnosis and treatment in man. The long taught and rather artificial clinical classification of the manifestations of the disease into primary secondary tertiary and quarternary periods induced a false conception of island-like or isolated phenomena unconnected by a continuous or an undulatory fluctuating give-and-take of attack and defense. Latency long a sacred retiring ground for *Spirochaeta pallida* within the human organism has in more critical recent examination turned out to be nothing but a clinical make-shift conception in which the fundamental continuity of the attack-defense process is main

tained simply at a low threshold of visibility. The latent patient is simply one without obvious symptoms, and the appraisal of his status by increasingly searching means reveals less and less of him so to speak, than was previously conceived. The primary stage of the disease, long thought of as one of limitation of the infection to the immediate neighborhood of the chancre and adjacent lymph nodes, formed a basis for the protracted adherence to a mistaken therapeutic conception of "abortive cure." The German syphilologists who were the authors of the concept were themselves in the end the most emphatic in repudiating it. Relapse and recurrence, long submerged in clinical importance by inadequate clinical examination, inadequate use of the darkfield, inadequate serologic exploration, are now coming into their own as in many respects clinically the most threatening and significant aspect of syphilis as a public health problem. They were not even considered in the old serological classification. In order to condense into the briefest possible space the modern conception of parallelism between clinical picture and pathologic background, Figure 7 has been devised. In this résumé remnants of the old "stage" terminology appear which are used to link the syphilologic parlance of the clinic with the fundamental immunology and pathogenetic conceptions of today.

FIG. 6.

SOME IMMUNOLOGIC PRINCIPLES

1. A immunity to syphilitic infection in man, in first instance, is unproved, probably rare, and unconvincing rather than badly.]
2. Within a few weeks after infection, however, immunity against re- or superinfection develops, which probably persists indefinitely, perhaps throughout life.
3. For reinfection to occur the disease must apparently have been cured before immunity has developed.
4. A nonreactive carrier state, in which the organism, though present, provokes no reaction in the host, is recognized in animals and probably exists in man.
5. Removal of the infecting organisms in large numbers by spirocheticidal agents probably interferes with immunity development.
6. The source of the immune state seems to be largely the local (chancre or local type) tissue reaction. There is, however, a humoral (?) element of as yet undefined nature, extent and significance.
7. The excision of foci like the chancre or the scar has no protective value. It could not generalize the infection, by removal of a major source of local defense.
8. The participation of defense groups of structures (skin, lymph nodes, test...) accepted but undefined. The reticuloendothelial defense is hypothetical.
9. No outright phagocytosis has been observed.
10. A granular rest or cyst stage of the organism is suggested by histologic observation and some features of the immunity.
11. Vaccines are ineffective, even increase susceptibility.
12. The humoral antibody and the "Wassermann" reagin are distinguishable (Kolmer et al.) (indistinguishable (Eagle et al.)).
13. An allergic or hypersusceptibility element enters into the tissue reaction of late syphilis (Kast meaning).
14. Healing is not proof of cure. Virulent organisms may be found in lesion scars of early syphilis.

The unit in this type of defense is the microscopical group of lymphocytes and plasma cells which collect in an infiltrative reaction around the spirochetes lying in the lymph spaces adjacent to the capillary vessels. The reaction set up in the vessels in the form of endarteritis reduces the blood supply of part of the parenchyma with ensuing degeneration. The lymphocytic infiltra

tion following identically the course of the typical reaction t all stages of the disease is gradually replaced by fibroblasts and fibrosis of the local focus ith a further loss of parenchyma results. The end-result of this microscopical focal reaction is, therefore *degenerative* and replacement

Fig. 7

COMPARATIVE RÉSUMÉ OF THE CLINICAL COURSE AND PATHOLOGIC BACKGROUND OF SYPHILIS

Cl ical Picture	*Pathologic Background*
1 Inoculation and Primary Incubation Period.—N clinical signs of infection.	1 Reproduction of organism going on in perivascular lymph spaces, with rapid distribution t lymph nodes, blood, spleen, bone-marrow etc., within a few minutes (imals) to t t three days after inoculation.
2. Primary Stag —Chancre usually p-pears t inoculation sit but with wide variation in local reaction even to complet absence Local lymphadenitis (bubo). Systemic symptoms (headache bone pains, et) may appear in advance f outspoken lesions. Blood W ssermann nd precipitation reactions begin t become positive	2. Lymphocytic and plasma cell infiltration produces papule and induration. Reproduction of organisms in chancre i t it height. Other similar foci developing throughout the body their number location, and activity proportional t virulence of organism nd peculiarities of host. Spirochetes present i blood-stream.
3. Early Secondary Stage.—Chancre begins to heal and widely distributed secondary skin manifestations develop with lymphadenitis, enlargement of spleen, bone lesions, changes in the nervous system, etc. Special structures may be ttacked, as eye, ear liver kidney ith serious results. Refractory stat develops, ith positive blood Wassermann nd precipitation reactions. Average infection up t second year	3. Local immunity reaction begins t destroy spirochetes in chancre and earlier secondary foci in viscera, as healing sets in. Enormous number of new foci established in skin, bones, lymphatics, viscera, etc. Systemic defence mechanism of agglutinins, lysins, etc., comes int play Lymphocytes disappear from healing foci, fibrosis occurs, organisms may be completely or partially destroyed or suppressed Foci in all stages of activity and decline throughout most of the body spirochetes numerous in blood-stream, innumerable minute spirochetal rests established in pericapillary lymphatics with larger probably temporary reservoirs in lymph-nodes.
4. Late Secondary Stage.—Secondary eruption disappears spontaneously systemic manifestations subside. Some symptoms from local foci may persist, such as palpable spleen or liver active but asymptomatic neurosyphilis, et Second to third year	4. Enormous destruction of spirochetes throughout the body complete in some foci, partial in others, the latter providing basis for relapse. Spirochetes become fewer or disappear from blood-stream with occasional showers. Systemic resistance mechanism reaches highest development toward end of this period, leading t latency
5 Early Recurrent Stage.—Any lesion of the primary and secondary period may reappear but especially lesions on mucous surfaces. Primary lesion and secondary eruption may reappear if temporarily aborted by treatment. Second to sixth year	5. Defects in local resistance with revival of partially extinguished foci and new showers of spirochetes with new crops of lesions developing from them.

Fig. 7 (Continued)

Clinical Picture	*Pathologic Background*
6 **Latent and Late Recurrent Stage.** Prolonged absence of symptoms, or periods of relative quiescence punctuated by relapses with lesions in bone, skin, mucous membranes especially. Lesions become fewer in number due to scarcity of spirochetes and more localized and destructive in habit, [illegible] due to developing allergy and vascular changes. Fourth to tenth year or later. **Note the overlapping time relations, in which almost anything may be expected at any time.**	6 **Spirochetes much diminished in number** and held in suppression or commensalism by local and general resistance, by immune and local defence at its highest development or by *nergy* (Chesney, Moore) tissue nonreactiveness. Local lesions may still flare up, however, discharging [illegible] organisms into circulation or lymphatic drainage area, starting new crops of lesions in susceptible tissue or reviving old ones. Patient may be rendered temporarily infectious to contact, or fetus may be infected, for example. Chronic inflammatory defence active, commensalism [illegible] foci may [illegible] strong general immunity but resulting in degenerative changes and fibrosis. Patient "living on his parenchyma."
7 **Late Syphilis, Gummatous Phase (Tertiary Syphilis).** Tumor-like lymphocytic and granulomatous masses appear in various organs. Central necrosis from endarteritic ischemia, extensive sloughs, much destruction of parenchyma and scarring. Lesions not usually infectious.	7 **Development of allergic (?) hypersusceptibility or effect of chronic vascular changes.** Violent tissue reaction to small number of organisms. Spirochetes in the lesions few and far between. Cutaneous allergy of nonspecific type demonstrable in many cases.
8 **Late Syphilis, Degenerative Phase (Quaternary Syphilis or Parasyphilis).** Degenerative lesions of cardiovascular and nervous system. Fibroses of parenchymatous structures, such as liver, spleen, pancreas, etc. Clinical changes and fatal result due to loss of parenchyma replaced by fibrous tissue [illegible] the blood supply [illegible]	8 **Spirochetes present,** at times numerous in some structures, but usually only to be found by special search of microscopic foci of tissue reaction in aorta, heart muscle, viscera, etc. Blood serologic reaction may be negative. Result: fibrosis, ischemia, necrosis.

of functionally active parenchymatous tissue [illegible] inert and weakened scar tissue takes place. These individual reactions and foci are almost infinitely numerous. They occur throughout the capillary distribution in the parenchyma of all the important viscera, in the heart muscle, around the vasa vasorum, in the [illegible] of the arteries, and in the nervous system. Their slow combined inflammatory degeneration ages the patient by inducing premature fibroses, and impairs the functional capacity of his vital structures by destroying their very substance and replacing it with connective tissue. The course or life history of these individual foci, varying between the extremes of healing and of rapid reproduction of organisms with distribution to the blood stream and lymphatic system at various periods throughout life, has been described. It is apparent in clinical experience that the tendency for such revival to occur with their ensuing relapses probably decreases considerably with the passing years. That it may, however, be [illegible] of relatively long latency is indicated by the reappearance of infectious lesions more than [illegible] decades after the onset of syphilis in patients who, in the interim, have remained entirely clear. The infection of the child in utero, the mother with latent syphilitic infection of a number of years standing, is also conceivably explainable through a transient spirochetemia associated with the revival of several latent foci.

Relapse is more prone to occur in man than in animals (Brown and Pearce) and is a function of decline in local tissue resistance which, however

is gradually enhanced by repeated increments in successive relapses until it becomes sufficient to hold the infection in check for a latent period varying in duration with the individual and with other factors such as injury While this resistance to multiplication of the organism and spread of the infection from any local focus is sufficient when highly developed to prevent clinical manifestations, the infection is not abolished but continues in a high proportion of cases indefinitely

In reasoning about the immunity developed in the later years of syphilitic infection, it should be clearly understood that its duration and the influence of individual constitutional factors are as yet imperfectly understood even for the animal, to say nothing of man. It is conceivable, and in fact the belief is to some extent supported by the work of Breinl and Wagner that there may be infected persons who develop only partial immunity such as the chancre immunity; that others may develop a complete immunity of less than lifetime duration and hence in later years may become susceptible to reinfection or more probably to superinfection, and that some persons may though rarely develop even chancre immunity of short duration and may as apparently chronic relapsers, be, in reality chronic superinfectors.

The clinical manifestations of relapse are of course legion and are essentially those attributable to the activities of the disease in the structures involved In the nervous system, relapse may be general or extensive or it may be so localized that there is no recognizable general meningeal or serologic response. Relapse may conceivably be fulminating and involve an entire organ mass, such as that of the liver in a colossal destructive revival of the infection. Relapse may be serologic in the recurrence of syphilitic reagin in the blood or spinal fluid, with or without clue as to the active focus from which the laboratory manifestations come. Relapse varies in type with the type of lesion of the phase of the infection, chronologically or otherwise present at the time. Thus, wholesale outbreaks of tertiary lesions may occur in late syphilis or they may equally well occur in early syphilis into which late "allergic" characteristics have been introduced by one or another circumstance. Infectious relapse is, of course a matter of great clinical and public health concern, and since it is largely manifested on the mucocutaneous surfaces and junction points, it is spoken of as mucocutaneous relapse. It is overwhelmingly an incident of the first two years of syphilitic infection in man but the more closely one explores supposed clinical latency in the first ten years of the disease, the more to his surprise does he encounter the isolated infectious relapse as a source of dissemination of the disease. The clinical characteristics of infectious relapse in man are especially considered in Chapter XIII and reinfection, which is often confused with relapse when it occurs within two years after the onset of a syphilitic infection is also subsequently discussed (Chapter XIII)

Treatment and the Mechanism of Relapse.—Treatment of less than curative intensity reinforces or operates through the bodily defense at any given point, destroying the multiplying organisms and permitting healing and disappearance of lesions On the other hand, it must be clearly understood that no treatment at present available is able invariably to prevent either the later reappearance of the original lesion or the further development of new ones when the relapse cycle permits the organism to resume multiplication and to overwhelm the tissue defense The deficiencies of short courses or scattered injections of the arsphenamines are notable in this regard. Relapse is particularly to be expected in patients treated with these drugs in subcurative doses, without proper reinforcement by the heavy metals.

Beckh, Barnett and Kulchar (1933) in summing the question, gave an interesting clinical review with reference to relatively small group of patients, indicating that the simultaneous use of arsphenamine and heavy metal, inadequate dosage of the arsphenamine either alone or feature of the so-called "continuous" treatment, contributed to treatment refractoriness, failed to control relapse, and increased the frequency of relapse in patients who became treatment-resistant because of the system employed. It should be understood that combined treatment here means simultaneous use of the arsenical and heavy metal and not alternation.

Relapse is critical if it involves a reviving focus in an important and poorly defended group of structures such as the nervous system. It follows therefore that a small focus of spirochetes in the meninges adjacent, for example, to the nucleus and trunk of the eighth cranial nerve can, upon their revival in the course of relapse, give rise to a fulminating and critical damage out of all proportion to the significance of the focus in the general display of reaction during the early months of the disease. The inadequate use of an arsphenamine in primary syphilis before the development of secondary lesions may thus, because of its interference with the development of the bodily defense, pave the way for a critical relapse dependent upon the location of the relapsing focus. Relapse tends to become malignant when it follows *insufficient allergy-inducing treatment* with the arsphenamines, which is rapidly destructive of large numbers of *Spirochaeta pallida* in the tissues and circulation. It was intimated in discussion of luetin that such a proteolysis seems to have in a certain proportion of subjects a tissue-allergy inducing effect. Thus when the inevitable revival of scattered foci following inadequate treatment occurs, each focus finds itself reproducing in an allergically reacting soil. The result is the appearance within a few months or even weeks of the primary infection of lesions highly destructive and fundamentally tertiary in character, dependent upon the premature induction of *Umstimmung* by treatment. Thus cerebral gumma, fulminating and fatal hepatorecurrences, destructive gummatous changes in bone and skin may be the result of treatment-induced allergy. This type of recurrence should be distinguished at least to some degree from the critical relapses whose anatomical location rather than their intrinsic destructiveness is responsible for the importance of the clinical symptoms. The differentiation, however, is theoretical rather than practical.

Is There a Relapsing Type of Human Syphilis?—It appears that the clinical conception proceeding from the opposition in the early arsphenamine days that an abortive and spirochete-destroying type of treatment by preventing a "healthy reaction" in the form of the full development of the secondary cutaneous eruption impairs the resistance of the individual to the disease is not without support. From studies in relapse it appears that the full secondary reaction exerts some inhibitive effect upon recurrence and that patients whose infection has been allowed a complete generalization and whose blood serological tests have become positive are distinctly less subject to relapse than are those on whom treatment is begun at an earlier stage. From still further studies it appears that there is in man a definite type of chronic relapser who, in accordance with the conception of Breinl and Wagner, never develops more than a partial immunity, or if he does develop it, does so only at the expense of so many relapses as to make him a constant and significant danger to the public health. These considerations are further discussed in Chapter XIII.

The actual figures in this matter (Cooperative Clinical Group) are as follows: Relapses were observed in 64 or 10 per cent of 810 patients with seronegative primary syphilis; in 105 or 8.8 per cent of 1203 patients with seropositive primary syphilis; and in only 4.16 per cent of 3930 of those patients admitted with florid secondary syphilis in the first year of their disease. Thus it would seem that the gradually developing resistance of the patient to the infection cuts the proportion of relapses 58 per cent from the maximum observed in seronegative primary cases as the patient passes to the eruptive secondary stage occurring within the first year of the infection. Of 121 patients who failed to develop secondary lesions until after the first year of the disease, a large proportion developed relapse (22.31 per cent). Mucocutaneous relapse is therefore twice as likely to occur in patients who developed delayed secondary lesions as in the seronegative primary case and more than five times as likely to occur as in the patient who develops normal early eruptive reaction. Studies by the group of the relative efficacy of treatment in seronegative and seropositive primary syphilis compared with secondary syphilis further indicate that the development of secondaries reduces the tendency to relapse.

THE PROBLEMS OF REINFECTION SUPERINFECTION AND CURE

The question of the cure of the disease in man as demonstrated by animal inoculation methods is therefore still *sub judice* and unlikely to reach determination within the next half century if not longer lacking investigation of fresh autopsy material under proper conditions of cold preservation and shipment to experimental centers. The evidence collected by Lake and Bryant and a brief paper by Chesney indicate that methods of determining cure in man have fundamental and serious uncertainties. "But why not accept reinfection as the proof of cure?" is the insistent question of the average syphilologist and clinician. It is experimentally demonstrable that much that would appear to be reinfection in animals is merely superinfection or a second infection engrafted on one which has reached the stage of asymptomatic latency. The alteration of immunity relations by treatment both in man and animals and particularly by incomplete or substerilizing treatment with arsphenamine may so distort the clinical picture that relapse reinfection and superinfection become indistinguishable from each other. Recent contributions on this subject include Kopp and Solomon (1939), Hahn (1941) and Allison (1942) (reinfection in congenital syphilis).

Syphilis binaria [illegible] (Hoffmann) is syphilis inoculated in birth upon an infant already rendered congenitally syphilitic by infection in utero.

Superinfection in Man.—Superinfection with generalization from an inoculation focus and the production of typical primary and secondary lesions with recovery of *Spirochaeta pallida*, has long been in doubt in man. If the work of Japanese investigators, including that of Akatsu, Yakota, Adachi and Hashimoto, is confirmed, superinfection following a course indistinguishable from reinfection or relapse will become an established entity in syphilis in man. Alleged reinfections occurring soon after the original infection will then be interpretable as relapses while those occurring years after the original infection when general immunity has perhaps begun to decline, will be interpretable as superinfections. This will inevitably mean that the final demonstration of cure in man will be forced back upon the studies of pathologic tissue and inoculation of human tissues into animals which must remain the province of the postmortem room and the laboratory inasmuch as they are obviously inapplicable during life. We may in a pessimistic mood regard ourselves as fortunate if syphilis-infected man is not proved to be, at once the world's most uncontrolled and uncontrollable relapser its most chronic

superinfector and is perhaps the most perfectly adapted asymptomatic carrier in nature

COLLATERAL INFLUENCES ON THE COURSE OF SYPHILIS

These for brevity are summarized from experience and the literature as follows

1 **The Organism** strain rate of reproductive activity route of inoculation site of inoculation size of inoculum

2 **Season Sunlight** ultraviolet (Harnes) hibernation (Jahnel) Experimental animal only

3 **Endocrine Hormones and Activity** (thyroid Pearce) theelin castration testosterone in experimental animal (Frazier and Hu 1941 Hu 1939 Kemp et al 1939)

4 **Diet** sunlight and summer feeding in animal only ((reenbaum) Earlier development of lesion in acid vs in rabbit (Nagai Ogata 1938-39)

5 **Avitaminosis** A and B in tabes (Moore and W)) B_2 in interstitial keratitis (Kruse Sydenstricker Sebrell and Cleckley 1940)

6 **Defense Mechanism** bone and skin involvement (Brown and Pearce Shaw) reticuloendothelial (elasmatic) activity lecithin injection etc (Morgan and Cunningham et al 1933 1934)

Age childhood mucosal syphilis especially frequent (Jean) more profound tissue reaction early syphilis mild course (Jean Morgan Smith in man Chesney in rabbit) Neurosyphilis more treatable (arsenic excretion spinal fluid Clausen and Jean Old age more florid early lesions.

8 **Race Negro** (Turner Johns Hopkins 1930 Hazen 1930) *Secondary syphilis* marked polyadenitis, frequent follicular and pustular syphilis, almost a monopoly of annular syphilids Negro female conspicuously predisposed to mucosal relapse *Late syphilis*—bone lesion exceed *neurosyphilis* latter only half as frequent as in white patient (30.5 vs 15.0 per cent females 22.5 vs 0 per cent) *Cardiovascular syphilis* twice as frequent as in whites *Leuk pl kia rare gumma f lymph nod* frequent *cerebral e darteritis* cerebrospinal syphilis as frequent as in whites tabes and paresis rare **African Negro** (MacArthur 1923 no visceral syphilis no miscarriages **Central American Indian** little visceral syphilis Shattuck **Arab** little neurosyphilis (Lacapere Bejel a special mild non venereal type (Hudson 1938) **Chinese** tabes and *paresis rare* (*Jeffrey and Maxwell*) *no spirochetes in spinal* fluid (Pearce Hu and Mu 1930) **Japanese** European incidence of tabes and paresis **Icelanders**, no syphilis For extensive review see Buschke and Joseph Jadassohn Handbuch **Animals**, see Rosahn 1933 Frazier and Mu 1930

9 **Sex** milder in women to the point of being almost a distinctive disease (Warthin 1928) probably due to biochemistry of menstruation and pregnancy comparable to nonspecific or shock therapy (Petersen and Hecht, cited by Becker and Obermayer 1940) immunity of heart aorta nervous system ovaries predominant though infrequent lesions of liver pancreas suprarenals. Repression of surface eruptive lesion more frequent constitutional symptoms tendency to lymphocytosis Lessened susceptibility to neurosyphilis 30 per cent (Stokes) to 50 per cent (Moore and Keidel) *Sex hormone*—estrinization of males produces milder course (Frazier and Hu 1941) Theelin same effect both male and female rabbit (Kemp Shaw and Fitzgerald 1939) Ovariectomy increases severity in females (Hu 1939) reversing Kemp and Shaw 1938

10 Pregnancy favorable influence on the course of syphilis first described by Hutchinson proven by statistical clinical studies by Moore (1922–23) by the Cooperative Clinical Group (Cole spokesman 1931) by Solomon (1920) and by Kemp and Menninger (1936) The course of early (secondary) syphilis is milder or suppressed in half the cases if infection occurs during pregnancy Secondary syphilis may be prolonged or the reverse (precocious tertiarism) may occur *Pregnancy prolongs latency over years may even lead to spontaneous cure* The skin, bones and nervous system are protected cardiovascular and visceral lesions more common. The syphilitic reagin fluctuates markedly in the blood and reversals to negative may occur spontaneously following delivery Ten per cent negatives may occur in florid secondary syphilis *Neurosyphilis is 3 times as frequent in males as females* though the incidence of abnormal spinal fluids early in the disease is the same in both Belote (1927) differed from Moore perhaps because of differences in approach and material (Moore had more colored patients though he subsequently proved this made no difference) Solomon found 44 per cent of women with tabes and paresis were nulliparae while of syphilitic women without neurosyphilis only 20 per cent were nulliparous The CCG showed relapse and progression to be nearly twice as frequent in non-pregnant as in women pregnant after acquiring the disease (7 per cent versus 4 per cent) The protective effect is more striking in Negro than white women. Kemp and Menninger found that coincidence of infection and pregnancy increased neurosyphilis, pregnancy in the sixth month to third year of infection greatly decreased it, with less beneficial effect if pregnancy did not occur until after the third year of infection. In late syphilis generally the CCG found the protective effect of pregnancy less marked or negligible

The animal experimental background (rabbits) has been established by Brown and Pearce (1920) and Chesney (1923) and Kemp (1937) "Pregnancy is good for syphilis but syphilis is *not* good for pregnancy "

11 Intercurrent Infection.—Broadly speaking, intercurrent infections acute, chronic, focal and general affect unfavorably the course of syphilis and its treatment.

Experimental Background Pearce 1928—vaccinia (virus infection) violently disturbs the immunity reaction and increases the severity of syphilis in rabbits Chesney Turner and Halley 1928—localization and development of syphilis lesions in granulating wounds and nonspecific inflammations.

Clinical Experience acute (especially epizootic) *virus infections* of nasorespiratory tract, and *influenza* affect *especially unfavorably* the course of neurosyphilis (particularly tabes) Responsible for treatment reactions especially dermatitis Pneumonia (lobar) may precipitate syphilitic pulmonary infiltration *Chronic infections* less clearly defined action largely debilitating, as in chronically infected Charcot joints, gall bladder disease renal irritability Chronic colitis maintains tabetic pains, etc. Hepatic infections interrelated with hepatitis and jaundice (catarrhal?) in syphilis and syphilis treatment. *Focal infections* notably teeth tonsils (Duke) maintain tabetic pains crises, retard healing of gummas osteomyelitis *Pyelitis* exaggerates tabetic symptoms though high fever may have nonspecific value *Malaria* may be followed by gummas of skin bones, interstitial keratitis *Biotropism*, Milian s term includes the ability of treatment for syphilis (especially arsenical) to flare nonspecific infections (streptococcal etc.) *Tuberculosis* disputed field usually affects the course of syphilis in various

ways Increased resistance to syphilis (Ohnawa 1022) Aronson and Meranze (1938) found that untreated syphilitic rabbits react differently than normal rabbits to intracutaneous injection of tubercle bacilli In 1940 they noted that local experimental tuberculosis pursue identical course in untreated syphilitic rabbits and in rabbits treated with treponemicidal dose of arsphenamine Evidence in man inconclusive so far Treatment for syphilis especially arsenical has marked nonspecific effect on some form of tuberculosis (not pulmonary) see Chapter V May also precipitate or activate latent tuberculosis (Padget and Moore 1930)

12 Heat, Fever (See also the discussion concerning the thermal death point of *Sp rockaeta pallida* see page 10) Heinman (1020) found chancres in rabbits healed and infection cured by tissue temperature of 104 F for 2 hours 107 0° F for one hour These observation are sufficiently confirmable in man (literature reviewed by Simpson W M, 1936) to justify rating elevation of tissue temperature by heat or fever from whatever cause or source as favorably influencing the course of syphilis at all stages Not all the effect is attributable to the temperature as such for surface lesion which do not reach such temperatures are sterilized nonetheless Lymph node spirochetes more resistant than chancre spirochetes (Boak Carpenter and Warren) Certain infection like malaria may produce paradoxically complication like interstitial keratitis probably for immunologic or allergic reason independent of the effect of temperature Morgan minimizes thermal effect as such in surface lesion rating other systemic effect of fever probably more important

13 Physical Strain – As distinguished from the effects of trauma, predisposing effect of overwork is best seen in increased frequency of cardiovascular syphilis in those doing hard muscular work (Cochem and Kemp 1937 also Lerkel 1930 Farmer found aortitis 11 4 per cent in medium and heavy occupation 8 per cent in light occupation aneurysm four times as frequently in heavy as in light work insufficiency three times as frequent in heavy as light work. MacArthur (1023) found rest and feeding alone sufficient to heal many lesion in African Negroes Therapeutically while there are many variants, rest is an invaluable adjunct in dealing with syphilis.

14 Nervous and Mental Activity —Largely clinical impression that paresis affects more often person of sensitive and labile temperament subject to heavy nervous strains (e g physician executives, etc) that neurosyphilis becomes symptomatic (especially tabes) after nervous and mental stress Possibility that the psychic stress occasioned by the social implication of the disease may affect its course responses and apparent symptomatology suggested by Pearson (1031)

15 Physical Constitution.—A yet relatively unstudied in man Brown and Pearce (1023) showed that constitutional peculiarities in litters of rabbits influenced the course of infection Fleming and Moore (1041) review the literature and propose and detail an investigative plan Lerkel found 67 5 per cent patients with aortitis of pyknic habitus (Kretschmer classification) Lazarovits (1032) confirming Tabes more severe in asthenic (slender) types (Curtius Schletter and Scholtz 1038)

16 Trauma.—Previously considered

17 Treatment More completely considered under prognosis Chapter V Summarized no treatment or very little treatment lead to spontaneous inactivity or arrest in an as yet undetermined (see discussion of Bruusgaard

statistics) proportion ranging between 25 and 35 per cent of cases (Chesney Morgan 1930 Stokes and DesBrisay 1924) Inadequate use of heavy metal with arsenical or inadequate arsenical alone predisposes to neurorelapse Precocious tertiarism may follow inadequate arsenical therapy Inadequate dosage may establish relapse tendencies and treatment resistance (Beerman, 1930) Small doses may establish hypersusceptibility to the infection (Bronfenbrenner and Schlesinger 1920 denied by Schamberg 1940) Inadequate treatment may slightly reduce adequate treatment markedly reduces the frequency of neurosyphilis (Kemp and Menninger 1936) All treatment reduces the frequency of neurosyphilis and the seriousness of neurosyphilis and cardiovascular syphilis (extensive review by Harrison, L. W 1940-Venereal Disease and Life Assurance—including summaries of Cooperative Clinical Group results)

CHAPTER II

THE CLINICAL APPROACH TO SYPHILIS

Obstacles to the Recognition of Syphilis.—Foremost as an obstacle to the recognition of syphilis during the period covered by our experience has been a low index of suspicion among medical men. Next in order comes the substitution of subjective considerations for the objective approach of thoroughgoing impartial examination. Subjective considerations include those personal to the physician, such as his estimate of the social status of his patient, prejudices regarding the moral significance of syphilis, and hesitation when it comes to involving himself in an intimate and personal issue with his patient on a supposedly venereal subject. It also includes the even more important subservience to the patient's subjective misconsideration of his chief complaint and history. Its also on and denial which mark the history-taking approach to diagnosis. As contributory to some of the current weaknesses of our clinical approach to syphilis, one should include a tendency to wait for signs dependent on consequences in our diagnosis rather than to seek out in prophylactic fashion the earliest inconspicuous warnings of the presence of the latent disease. One should also emphasize the loss of respect for clinical as compared with laboratory evidence and the substitution of routinized tests for critical thinking which has marked the medical practice of the first years of the twentieth century. Finally, it is necessary to point out the weaknesses of a single method of approach to the disease and the necessity for attacking it from a number of diagnostic angles simultaneously if the highest possible accuracy in diagnosis is to be attained.

Suspiciousness of Mind.—Alert suspiciousness of mind, necessary though it may be in all medical diagnosis, is an absolute prerequisite to the successful detection of syphilis. This does not mean a mere vague awareness of its existence, such as an adequate training may substitute for definite knowledge. It means a sharp positive consciousness of the imminent possibility of encountering it, an alert sense of nearness such as is experienced by the hunter stalking big and dangerous game. A zest in the ferreting out of the obscure, a positively detective zeal in the running to earth of this most subtle master of the dissembling art, is the foremost asset of the clinical syphilologist. That this ultrasuspiciousness has its drawbacks is conceded, and they will be considered later. On the other hand, the physician who has a psychical blind spot for the disease sustains a life handicap as a diagnostician.

Alertness toward syphilis is effective only when it is chronic and consistent. The disease takes constant advantage of that type of diagnostician in any field whose search for it as a factor in his work is confined to occasional shake-ups following a report that some colleague more alert than himself has checked up one of his cases and by identifying the unsuspected syphilitic factor and by applying treatment has scored a triumph. Such an experience yields only a portion of its teaching value if the losing side is merely inspired to add another element to its routine procedure, as distinguished from its mental attitude—such, for example, as a Wassermann test on all patients showing edema of the nasal mucosa, or bilateral hydrarthrosis, or what-not. Valuable as some routine procedures are, failure to recognize syphilis in a given instance should lead the modern physician to do more than blindly enslave himself still further to any single routine aid. It should inspire him to re-canvass and furbish up his clinical acquaintance with the disease.

Low Visibility and Wide Dispersion.—*A low index of alertness or suspiciousness toward syphilis is* in the existing situation of the profession, a natural consequence rather than a fault. Syphilis is a disease of low visibility and wide dispersion of manifestations. A large part of its course is run below the threshold of attention. It has two relatively obtrusive periods, that of the primary sore and secondary eruption and that of terminal complications. In the former phase only half (55 per cent) of the diagnoses are made.

With the growing realization that the disease is often anything but obtrusive even during these outspoken periods of its course, it has become evident that in syphilis the physician has to deal with an almost unique diagnostic problem. Cause and effect, when the former is not entirely concealed, are often separated from each other by years and even decades of symptomless and signless latency, during which only routine probings with diagnostic tests and the most vigilant search for marks on a seemingly flawless surface enable us to detect the underlying pathologic process.

The nature of syphilis as a disease, then, has been a principal cause of lack of suspiciousness among diagnosticians.

Subjective Considerations.—*To the critical judgment, syphilis has of* course its moral phase, precisely as it has an ethical, an economic, and a social phase. But the effort to mix the standards of moral judgment with the medical issues of detection and treatment of the disease seems to lead to nothing but befuddlement.

One sees seriocomic instances in which capable clinicians betray the tenor of their thought by a sort of unconscious standard of reference, in which one Wassermann test will convict a laborer over his own denial, two will make a case against a banker or a railroad president, but three successive positives will scarcely convince the medical advisor of the guilt of a clergyman. The thin veneer of appearances, the air of prosperity, the evidence of education, an unimpeachable ancestry or the appeal of innocence constantly deprive patients of even the elementary investigation of the etiologic possibility of syphilis, to which, when rightly thought of, they are absolutely entitled. *So long as an investigation for syphilis appeals to any group of medical men as an affront, syphilis will elude their vigilance.*

The Nuisance of Syphilis.—There can be no doubt that to find syphilis at *the root of a diagnostic problem spells work, annoyance, and embarrassment.* The stigmatization of the disease by social tradition reflects itself in our search for it in patients. Even an experienced syphilologist finds himself at times puzzled to devise a tactful approach in a given case. If an experienced searcher meets such difficulties, *how often will the inexperienced be rendered lukewarm or actually deterred.*

The tradition of taking a venereal history is now well established, but the act itself is often superficial. *Unpleasant explanations may follow on the heels of positive findings in many cases.* The modern obligation to ferret out the ramifications of the disease in the family when it has been found in any one member is an added complication that discourages a too eager search. If the disease is found, there comes treatment with its complex modern standards, with which too few physicians can profess even a measure of confident familiarity. It is no wonder that a sort *of syphilological [illegible] or [illegible] comes to affect some of us after a few experiences with the* nuisance of syphilis in a diagnostic complex.

Overemphasis and Underemphasis.—On the other hand, rightly viewed, the *recognition of syphilis is a positive relief to the puzzled examiner.* This sense of relief has, too, its undesirable side. It becomes a diagnostic straw to clutch at, a lifebuoy which can float the most astounding weight of heterogeneous or puzzling symptoms. In the presence of a positive Wassermann

the th rey or tel fract w h novel t nt yp l l Much of the ph m these rules of thumb t the pres t l t b l e l l l vated n men i e are to the search gregory of mos beh g e m d m g d q reach It is t m ry e t forget e not l real e th t there m y be ph l l psane t t nes d g e h hard edge m ber see ar l heh merge l never en t d l e e alen h f e Il concept of ph l f h special

Clinical and Laboratory Diagnosis. Cl n al ar l laboratory diagn es in medicine are too oft n p k n f a m inta ning a pe e of tacit rivalry not to say antag ni m toward each ther Th y are in f t c mpl mentary and sul ject to th sam human l mitati n Th trend f th la t f w years l unquesti nal ly been t erat th lal r t ry and l preciate the clinic While on mu t c ceed the p sitive n ed f r s tematic use of certa lal rat ry t t am unting in f t t n it ne application in certain a pect of syphili the diagn stician l ould n er f rget that the ubstitution of mechanically rdered te t f r a frame f mind re ult in some of th gr est syph l d gical diagnos in medicine l e all it s lu any procedure which substitut a te t tube rea tion f r a prim ry acuteness of perception debases the cl nician and cost him ften in the end m re ff ciency an l self-respect th an it accuracy n l ea s acces l il ty can ev r ju t f The al al condition of course prevail where the c ll f r the regular an l s t matic use of th serologic test i a reasoned pr cedure based on th cl nician s intell gent percepti n of th se peculiarities f the l sease wh ch make it valuable and perhaps even routinely les rable But the thing that comes first i alertnes t ward syph lis The use of th test routine or pti nal f ll w th l agnostician logical appreciati n f the place it h ld in hi armam ntarium and in the natural hi t ry f the l sease

Preventive Outlook In n f ld f medicine i the l abit of prev ntive thought more needed than in l aling w th ph lis The con tant eff rt f the practicing phy ici n the diagnostici n an l the therap t hould be t get one tep nearer the beginning f each manifestat n each accident than did hi predeces or f th year r decade bef re The treatal ility of syphil much greater than that f many of the m re pul licly l scu sed scourge of mankind and it controllal il ty a an infection are ich th t every expend ture of effort in thi lirecti n yield rich return Th treatment of late yphili i the detecti n of early an l latent sy l il an pl en m th t will be repeated empha ized l y the mat rial f ubsequ nt ch pter The Wa sermann te t on the patient with a palpabl li er nd n c mpl nt the pinal fluid te t on the "nervou break l wn th recognit n f th rly tambour secon l sound over the aortic area rath r than the heaving precordium loul le murmurs, and enlarged heart of f ve years later th treatm nt of the yphil tic mother in tead of th child i th essence of n l rn cl nical yphilology

Multiple Attack and Collateral Evidence It at t mes still difficult for the physician sharing the common desire of human nature for tou h tones and "open sesames to realize that yphil will n e wh lly yield to a single diagnostic key The ancient clinical yphil l gy n r xpected it It wa f r the new syphilology to propose first th W sermann and then the luetin tests as diagnostic infallil ilities Critical rev i ion h reduced our hopes toda to the point where *in my estimation it i fair t ay that no ingle procedure* can be expected to identify more than "3 per cent of the syphili which present itself for diagnosi in the average medical clinic T be sure this record is n discredit to the tests which are respon ible f r it Few ingle modes of approach

to any problem in disease can boast so high an average efficiency as the blood Wassermann test, for example. But in raising the efficiency of diagnosis as near to 100 per cent as possible advantage must be taken of all the resources of attack which modern medicine provides and not of one or two alone.

Syphilis is, fortunately, seldom a completely monosymptomatic disease, so that it is usually not too laborious a search to find the positive elements in a complex. It tends, as will later appear in its later phases, where the maximum diagnostic difficulties occur, to be polysymptomatic in its expressions, so that if one line of investigation yields a negative result, another may yield positive. The presenting phase may, however, have a doubtful specificity, as when a patient enters with symptoms of aortitis, negative serologic reaction, no history of syphilis, and generally negative syphilological findings up to the point where one reaches the examination of the spinal fluid. As soon as this is done the familiar combination of cardiovascular and neurosyphilis becomes the presumptive diagnosis following the identification of positive and specific changes in the spinal fluid, even with a negative neurological examination. The identification of much of the syphilis of internal medicine resolves itself into such a search for collateral evidence. The collateral evidence may appear at once in the form of a positive serologic reaction identifying a lobulated liver as syphilitic in origin. On the other hand, a diagnosis may not be reached short of half a dozen procedures, and may even then elude the clinician only to be brought out later by the resolving power of time in the form of repeated observation.

The Problem of Pseudosyphilis.—The decision to leave unaltered in revision the foregoing pages on the clinical approach to syphilis must be qualified by the *changes which are taking place in the viewpoint of the practicing* physician toward the disease. Emphasis on the importance of a high degree of chronic suspicious alertness toward the omnipresence and the difficulties of recognition of syphilis is undoubtedly still well placed, but it is to the credit both of the revived teaching of syphilology and of the conscious effort of the practicing physician to keep abreast of the best his time affords, that the proportion of undiagnosed syphilis is probably materially on the wane. Coincidently with this improvement in diagnostic standards there is developing the usual secondary wave of qualification and reappraisal of diagnostic methods on the one hand, and a wave of overenthusiasm in the use of certain of them, on the other. There can be very little doubt that today, as a result of wholesale application of single diagnostic procedures, there is a good deal of syphilis diagnosed which is not syphilis at all. Error in the performance of some essential test throws the diagnostician off the track and raises suspicions which can be stilled only by the institution of treatment as a therapeutic test, if nothing more. On other occasions the extraordinary facility with which syphilis apes every disease in any field of medicine, leads inevitably to a borderline of confusion in which not only one but a number of really very presentable reasons can be urged for regarding a patient as syphilitic when, as a matter of fact, he does not have the disease. The roentgenogram of a bone, the feel of a liver, a sequence of eruptive events, an incisor tooth, may be the point *on which a diagnosis seems to turn. The large proportion of pseudo-*syphilis probably takes its origin, as Mitchell has pointed out, from partial or weak positive serological tests reported by laboratories not acting under appropriate syphilis clinic control. A proportion of these, steadily diminishing in importance with the perfection of serological tests, represent biological false positives and the nonspecific margin of error of even the best test procedures. Nonspecific therapeutic tests (see p. 151) in which the clinical response of a condition other than syphilis to treatment usually regarded as specific for syphilis itself constitutes the second group of mistakenly diagnosed cases. The third group rests upon the misinterpretation of clinical signs. The

student of syphilis once he has developed the alertly suspicious mind must certainly be on the lookout for the pitfalls of hypersuspiciousness. There is no doubt that the place of syphilis in general medicine can be exaggerated by the enthusiast who does not maintain a system of balanced check upon his interests and his ferreting instinct. On the other hand, the pleasure of bringing to book by the detection of some egregious "flunk" the ultraconservative mind which defines "syphilologist" as one who calls everything syphilis is the keenest in the whole realm of intellectual pursuit. The expert surrounded by an elaborate machinery and constantly confronted with the extraordinary versatility and imitative capacity of syphilis encounters his pitfalls in a tendency to excessively fine-spun decision. Fear on the part of the average physician of overlooking the possibility of syphilis leads to such tragically familiar mistakes as treating epithelioma of the tongue as syphilitic to the point of fatal metastasis, or the performance on a young man with a herpes progenitalis of multiple Wassermann tests and darkfield examinations, two spinal punctures, a circumcision and a biopsy which removed a very fair portion of his glans penis. Of the very puzzling and often serious problems which confront the consultant as a result of serological inaccuracies the following example introduced here to whet the interest of the reader in the more critical considerations of Chapter III (biological tests) is offered.

A man of fifty-three whom Stokes personally examined in March, 1917, exhibited the clinical symptomatology of a very early paresis with typical and unmistakable serological changes in the blood and spinal fluid, including a positive Kolmer and Kahn test on the former and a positive Kolmer-Wassermann with a classical colloidal curve on the latter. Owing to some technical difficulties encountered by the home physician in treating his case on recommendation, he had only a very moderate amount of treatment while away, which could not possibly have changed his serological reaction materially. To the great surprise of Stokes, a letter was received from the physician who dealt with a technical complication, which read as follows: "He was suffering from an injection abscess of the buttock. We opened it and drained about 2 pints of sterile pus. He has made a good recovery. His blood and spinal fluid are negative. If you have any suggestion relative to future treatment I would welcome them very heartily." Experience with the biology of the disease, that stabilizing and determining factor which often saves the day for the consultant, led J. H. S. to doubt the accuracy of this report on blood and fluid though he had every personal confidence in the man who quoted it. On his insistence the patient revisited him at once and a second spinal fluid examination was performed by J. H. S., the fluid from which was examined by two laboratories, yielded results practically absolutely identical, both on blood and spinal fluid Wassermann, cell count, globulin estimation and colloidal test, with those positive results which he had obtained in the first examination. J. H. S.'s situation as consultant now became one certainly not likely to endear him to the home folks, for "who is less beloved than he who revealeth an error?" If, accepting the report of the home physician's hospital on this serology, J. H. S. had proceeded to advise further in regard to his treatment without re-examination, the patient would have gone from bad to worse. Contrary to general belief such gross and obvious mistakes are much too frequent. Only a most devious explanation involving hypothetical possibilities such as the transient effect of a Netter abscess, saved the face of the situation in the eyes of those concerned. This patient's life literally hung on the inaccuracy of this report. The abnormal spinal fluid findings have been confirmed by a third examination and two years of consistent energetic treatment has finally yielded a good therapeutic result.

In another instance five different Wassermann tests, supposedly divided between two laboratories, were all sent to the same laboratory inadvertently and all were returned strongly positive. The institution of treatment so changed the diagnostic perspective in the case that it probably never will be possible to determine whether or not this patient has syphilis, but every evidence points against it. His chief complaint of diarrhea, which was, upon the finding of the false positive Wassermann, interpreted as syphilitic in origin, is one of the rarest complications of the disease. The clinician's examination of the case came to an end when the positive Wassermann was discovered and it was only subsequent investigation over the head of the positive blood test which proved that the diarrhea was amebic in origin. This man was by no means the victim

of diagnostic incompetence and his serological tests were performed in a private laboratory under excellent medical direction. The more complex possibilities of pseudosyphilis, based on combinations of clinical and serological signs, are illustrated by the following case. A virgin of thirty-six, in previous good health complained of what was thought to be urethral caruncle. Immediately following the next menstruation an acute urethritis developed, the smears showing a short diplobacillus in two competent laboratories. Following the use of an enema the rectum apparently became infected with the same organism, giving rise to bleeding and pain. The vagina became involved, with severe pain and spasm, and the second menstrual period produced only a small amount of bloody discharge with a fetid odor. In the ensuing three months the vaginal condition improved under local treatment and then suddenly an eruption appeared, accompanied by vulvar itching. Six months later after an interval of comparative comfort, a gingivitis appeared followed by symptoms of stiffness and swelling of the neck glands and pain in both shoulders. A glossitis followed and a painful spot appeared in the left chest. Coincidently a general eruption developed which was of a florid red, itched somewhat and was accompanied by mouth lesions from which a distinct pellicle or skin could be picked. Patches were most numerous on the gums. A sore spot appeared on the head in the left frontal region with a visible swelling accompanied by a fever to 101 F. A skull roentgenogram, taken three months later showed the typical charnation of the inner table frequently observed in lues. The serological history in this case followed an up-and-down course with curious inconsistencies and reversals not in keeping with biological expectancy in the ordinary course of the disease. Even a spinal fluid examination, which was negative to the Wassermann and colloidal tests, showed a slightly increased cell count, a finding which had been noted by Herrick in nonspecific systemic infection. Diplo-organisms were again found in a vaginal smear and the patient's fever continuing, treatment with an arsphenamine was begun with very slow and atypical response. The upshot of the entire case was a complete recovery and the syphilological evaluation compels the conclusion that she had never had the disease. None the less, at one point after another during the course of her nonspecific infection, individual isolated signs or serological returns could easily have been interpreted and in fact were interpreted by competent observers as evidence that she had a syphilitic infection. This case now of more than four years standing has never at any time given further evidence of what might be interpreted as a latent or inactive syphilitic infection.

The Intuitive and the Problems of the Consultant.—All the cases above described, and particularly the last one, furnish excellent illustrations of both the logical and the intuitive phases in the diagnosis of syphilis. Desirable as it is that medical acumen and procedure be free from partial and ultrasubjective interpretations, it can never be wholly freed from them. Intuitive diagnosis has a legitimate place in the identification of syphilis when it is the product of long experience with both the broad aspects and the special relations of the disease. In one particular field, that of the recognition of heredosyphilis, for example, intuition holds a peculiar almost unique place among diagnostic criteria. Much as one might wish to eliminate it, the intuitive is a factor in every diagnostic decision which involves the weighing of evidence. It gives to the pronouncements of even the most objective of syphilologists the same temperamental and personal quality which enters into all medical judgments. Realizing this, no individual clinician is living up to his obligations with respect to syphilis who is not questioning himself searchingly from time to time as to this factor in his work, and as to the consistency and logical development of his thoughts concerning the disease. Just as the farmer through lifelong contact with growing crops, and the bacteriologist, as in the case of Noguchi, or the parasitologist in the case of Schaudinn, reaches conclusions which arouse, sometimes, the skepticism, sometimes the surprised admiration of the bystander so the decisions of the consultant in the syphilological field, in part subconscious and based upon an intuitive and experiential knowledge of the biology of the disease, may at times fail of rational analysis even though time and the course of events prove them to be correct. The best antidote for a disposition to be overintuitive in such a capacity is the determined writing out, in notes and correspondence of the full detail of logical analysis applicable to the individual case.

THE EXAMINATION OF THE PATIENT

The ideal approach to a syphilological examination is purely objective. In other words, a complete study of the findings precedes the taking of the history irrespective of the chief complaint. The practicability of this method of approach under office conditions may however sometimes be questioned. The taking of a history if it is painstakingly done and follows all the essential

leads in the nece sary detail provides an acquaintance with the patient that greatly a sists in the final appraisal of the case After a con iderable experience with various printed form technics of taking the hi tory of the syphil s patient, we have finally aband ned tl m in favor of a mimeographed outline or desk card containing the lead which hould be foll wed The history i then tak n

Fig 12

STANDARD GUIDE SHEET SIGMA HISTORY

C C (chief complaint) St t the purpose of the patient i seeking examination, the chief mpt m if the durat n f the infect n ith date of primary and the preliminary di gno tic impression

F H (f m ly h t ry) I age t parent l marital hi t ry miscarriages nd stillbirths, nervous disease ascula d sease renal dise se serious infect on including tuberculo nd rthritis met l lic d sease including thyroid, diabetes allergic disease (eczema, thma, urticaria, ha fe er migraine) habit (lcohol, sexual, f d)

P H (pa t h t ry) Serious illness marri l nd childbirth operations i juries, previous medical ad ce tropical or foreign residence hab ts, drugs (include al hol

I T (present t uble

1 Chancre nd secondaries ith dates constitut onal symptoms morphology generalization

2 Sexual contacts, source of infection

3 Present g mptoms

4 *Inquire further relative t the following mptom*

Gastrointestinal symptoms including vomiting

b Lues (headache b ne pains, tabetic paresthesias, including umbness, girdle sensation, shooting or lightning pai s, abdominal ttack)

Visual nd ud t ry disturbances

d Bladder nd genit urinary disturbances cluding loss of l bido nd potentia

e C it (especially after da k)

f Mentality (inquire of escort ell patient, privatel)

g Cardio ascular arrange or mpt ms (presternal or arm pain, effect of exercise yspnea, especiall nocturnal, palpitat on)

5 Previous ad ce and management Summarize al dable documents, including serological test result Outline t date follows, for example

1918 J Chancre glans, no darkfield, BWR pos.
J t March 1 ill (dat of preparation if vailable)
Ma h t April Ss inj Neo (?) dose ( ), interval seven t ten da
April 15, BWR neg
1919 20 Three BWR neg
1921 Feb BWR pos 8 labs (1 Kolmer nd Kah 1 th p)
Fel 17 to March 30, 19 j Neo 0 9 ( )
April 7 BWR neg Lapsed
1922 26 Four BWR neg on mtist
1927 Genl exam X— Clear BWR p CNS neg CSF cell pos X— Clear
See letter
Ma t Jul Ten AB, 80 Hg succin X Cl r
July t Sept 60 ml
Oct BWR pos CSF p
Oct t No Malaria, 8 ch lls, severe reaction
1928 Jul CSF improved, WR kol 20100, glob 1 plus, cells 8, gold 0000110 0
BWR kol 22
1929 Jul CSF neg N nterma R

6 Comments on re ctions and ymptomati progress

7 R marks. Lea 3-inch space for consultant notes

with the card bef re the inquirer the lead are noted as they are taken up on the blank heet and the data written in by hand Such a work sheet or standard history guide a used in our offices and clinic at the University of Pennsylvania is gi en in Fig 12

In general it may be said that the trend of the history-taking for early syphili should be toward specially searching inquiry into the circumstances

time relations and persons involved in exposure the onset and presence of lesions of the mucous membranes skin anus and genitalia the family responsibilities and contacts involved the possibilities for the future such as engagements to marry informal sexual partnerships and so forth the darkfield serological and other examinations on which a previous attempt at diagnosis may have been based the time relation of these procedures to each other to the exposure of other individuals and to the institution of treatment and the actual facts in detail as to drugs dosage time intervals between treatments, number of treatments per course and especially rest periods without treatment or lapses from treatment on the patient s own initiative These time relations are of vital importance in estimating the status of any given case from the standpoint of modern therapy It is for this reason that the previous advice and management of any given case is summarized on a chronological basis in Fig 12.

The inquiry and examination in patients with latent syphilis (no cutaneous lesions and a duration of a year or more since infection) should concentrate on the time relations and general adequacy of previous treatment, on marital and other sex contacts, the status of the family and evidences of recurrence, clinical or serological The matter of a complete spinal fluid examination must always be carefully inquired into.

The emphasis in patients after the fifth year or even before should be upon the symptomatology arising from important viscera and systems in process of impairment or actually injured by the disease. Gastrointestinal symptoms and jaundice deserve special inquiry the former because they are the expression quite often of injury to the nervous system rather than to the gastrointestinal mechanism itself The cardiovascular and nervous systems, the two great fields of critical damage and often obscure symptomatology must be painstakingly gone over if the weaknesses of our present poor showing in the matter of prevention are to be remedied These lines of inquiry are outlined in Fig. 12 (Item 4 under Present Trouble)

The Physical Examination for Syphilis.—It is impossible for one thrown into intimate contact with syphilological diagnosis to do otherwise than reluctantly concede the truth of the dictum sponsored among others, by Billings, that one of the principal defects of medical practice at the present time is failure to examine the patient adequately The baseline physical examination of the patient at the outset of his infection is the starting point for all subsequent estimates of clinical progress, favorable or unfavorable Yet how often on feeling a palpable liver for the first time or noting a definite hypertension with accentuated aortic second sound does the consultant find himself without a point of reference in the form of a previous properly performed physical examination on which to base his decision as to whether symptoms and signs which he detects are new and due to the advance of the disease or old and related to secondary or adventitious causes

Figure 13 presents a standard guide sheet which is the result of fifteen years of effort to reduce the leads and the essentials in the examination of a patient for syphilis to minimum essentials and the proportions of a card for desk reference. It will be noted that the arrangement of the examination is by systems rather than by regions. While this might seem at first to lead to reduplication of effort and movements on the part of both patient and examiner the difficulty we have experienced with it on this score is negligible in comparison with the very great advantage derived for the consultant from

the sorting out of findings under a satisfactory scheme of classification for appraisal. The use of such a schedule of examination need not in any way interfere with the extension of any particular lead in whatever direction the findings in the case may seem to indicate Thus, for example, it is not proposed

Fig 15

STANDARD GUIDE SHEET SIGMA PHYSICAL EXAMINATION

On Completing Examination, Underline All Positiv Findings in Red. Record All Negatives. Sign Reports with Name Not Initials.

D S. (Descriptive summary) Terse t or three-line summary of patient as hole
T P R. (Temperature, pulse, respiration.)
Skin and Scalp ("Not the mechanical warm, moist nd elastic.") Observe vasomotor reactivity also.
Mucosa Buccal, lingual, gingival, labial. Nasal orifices and septum.
Teeth and Tonsils.
Palms and Soles.
Anus and Genitalia (see Fig 14) Palpat prost t if ndicated
Lymphatics.
Bones, Joints, Frame, Muscles.
Endocrine. Signs of thyroid or other dystrophy
Liver and Spleen. Use Middleton maneuver (forearm under back t raise liver edge)
Other Abdominal.
Lungs. Auscult and percuss if indicated only
Cardiovascular
Heart and Great Vessels.
Inspection.
Percussion dimensions in cm.
Apex position and impulse.
Isthmus and base. Neck.
Palpation, pulsations and thrill.
Auscultation. Muscle and valve sounds, A2 or P2. Murmurs, shocks, adventitious sounds. Check lying, sitting, and leaning forward.
Blood pressure both arms reclining
Peripheral Circulation.
Radial, anterior and posterior tibial and capillary pulse. Condition of vessels. Venous prominence. Femoral sounds. Corrigan. Condition toes and fingers.
Central Nervous System. Inspection for atrophies, trophic changes, functional disorders, personality
Eyes. Pupillary reactions, a, c, and d ptosis, extra-ocular movements, nystagmus, visual acuity by rough test (type), visual fields (rough) Lens for opacities, synechia. Ophthalmoscope for "normal" survey
Ears. Test ith w tch.
N VII. Whistle, nk, grin
Deep Reflexes. Biceps, triceps, knee, Achilles (take kneeling), umbilical, cremaster
Motor Function. Extension, flexion, arms and legs against resistance. Test feet and grip, both sides.
Babinski Reflex.
Ankle Clonus.
Special Orientation. Finger-to-nose test. Heel-to-knee test. Romberg test. Gait
Adiadokokinesis.
Sensory Perception. Muscle-joint sense (see above) Vibration sense (C-128 fork over malleoli and olecranon processes) Pinpoint and touch. Extremities nd trunk, cheeks and forehead (If hurried, do lo er extremities.)
Speech Tests. (The "R tests)
Handwriting, Memory
Mentality An excellent test (Foster Kennedy) is to have the patient write an unprompted letter of two or more pages.

to regard the survey of the central nervous system here given as an adequate neurological examination for all differential diagnostic purposes The examination as given however reveals clearly the types of abnormalities characteristic of neurosyphilis in the large majority of cases and brings to light in a

search thus directed enough suggestive clues to protect against the majority of diagnostic pitfalls provided each special clue is followed up when indicated

The time required under office conditions for an examination of this degree of thoroughness ranges from thirty minutes to two hours and is materially shortened as the examiner's experience grows. The instruments required aside from those for distinctively laboratory manipulation such as darkfield and blood specimens for serological test, include stethoscope steel tape soft rubber reflex hammer tongue depressors, flash light, tuning fork (C-128) and a pin stuck transversely through the end of a wooden applicator for testing pain-touch differentiation



Fig. 14.—Routine examination of anogenital region in women. A speculum examination in the lithotomy position is desirable if there is marital introitus and suspicion of early syphilis. A responsible adult woman should be present at the examination of girls under eighteen years of age Rubber gloves should be worn.

Emphasis should be placed on the conditions under which a physical examination for evidence of syphilis is conducted. Good light is essential particularly for inspection of the skin orifices and flexures of the body The ideal light is north daylight but a tungsten daylight bulb can be substituted by a practiced examiner The light should be on a movable stand which should be so placed that the regions mentioned can be absolutely flooded with illumination Not only does the disease escape unrecognized when examinations are conducted under poor or improper lighting conditions, but the examiners are themselves subjected to dangers which they little realize The macular secondary syphilid is difficult enough to see under the most favorable conditions By artificial light it is invisible five times out of ten. Shadows cast on impor

tant points result in serious errors in diagnosis, and in contact unawares, with lesions that swarm with the *Spirochaeta pallida*

We have known a trained observer to pass the bare fingers over a condyloma on the fourchette which even his preliminary inspection had not disclosed because the patient was examined by a powerful overhead light a little too far back with reference to the position of the patient so that a tiny lunette of shadow hid the lesion.

Fig 15

THE CARDINAL SUSPICION AROUSERS OF SYPHILIS

Symptom	Sign
1 Miscarriages and stillbirths.	1 An indolent lesion with one-sided local lymph node enlargement anywhere
2. Protracted headache	2. The genital or anal erosion, ulcer papule ring, button or scar
3 Pseudotuberculous and pseudorheumatic symptoms in the twenties.	3. Patchy hair loss.
4 Hoarseness and aphonia (protracted)	4. Any widely scattered nonvesicular eruption lasting more than two weeks.
5 Pain (especially nocturnal) persistent in isolated bones and joints.	5 General lymph node enlargement.
6. Failure to heal, especially skin and bone.	6. Palpable induration and arciform configuration with scar in any skin or mucosal lesion.
7 Persistent vomiting	7 The atrophic smooth or deeply scarred, or heavily leukoplakic tongue
8 Nocturnal dyspnea.	8. The locally enlarged, thickened, or tender bone especially tibia or shoulder girdle
9. Periodic vomiting.	9 "White" or phlegmonous swelling of any joint or pair of joints.
10 Failing vision.	10. Skin adherent and scarred over bone
11. Double vision.	11 Palpable liver or spleen.
12. Sticking, sharp or "lightning" (cord) pains.	12. The "tambour" aortic second sound
13. Bladder hesitancy leakage	13. The pupils, unequal, slow or fixed to light.
14 Neurasthenia and conduct slump in adults, especially after 40 years of age	14 The dropped eyelid.
15. Pink eye lasting more than 10 days.	15. Absent A. and K. reflexes.
16. Sudden deafness.	16. The positive Romberg.
17 Conduct slump in a child.	17 The sudden cord paralysis.
	18. The caved or sunken nose
	19 The teeth—Hutchinson upper central incisors, Moon 6-year molars.
	20 The facies of congenital syphilis.

Those who desire line-drawings of the technic of regional examination will find them in the first and second editions.

Certain significant points in examining the skeletal system include emphasis on the tibia as a frequent seat of osseous change The fusiform thickening of the middle third of the bone should be felt for by passing the bone between the thumb and first two fingers (Morton Smith's maneuver) and feeling for the rounding of the anterior face, as well as anterior bowing of the edge with the flats of the fingers or hands. In every inspection of the patient it is wise to

Fig 16.

ITEMS EASILY OVERLOOKED OR MISINTERPRETED IN THE PHYSICAL EXAMINATION FOR SYPHILIS

Body Region.	*Early Syphilis.*	*Late Syphil*
Th p llml y scrutiny	Signs of emotion personality appraisal economic status family comrades, contacts. Eyebrows, hair eight loss, anemia, stiff or impaired joints, control of lips and yelids (N ll).	Same early syphilis, plus expression, condition of clothing, oice and speech mental response Odor, scars, photophobia, corneal louding, pupils, hearing, pallor cyanosis, tremor edema, lip smacking, neck pulsation, gait, overweight.
Skin, general (including scalp)	Mottled or spotted skin nd neck. Papules t ngle of mouth Erosions on lips. Ringed lesions. The fleshy or indurated feel of lesions. Faint rashes on tru k. Faint eruptions, rists and forearms. Goose flesh appearance (follicular lesions) and grouping in lesions.	Chronic small ulcers or groups of ulcers, nodules or scars. Ringed, arciform nd kidney-shaped lesions and similar scars, thin nd paper like or in hich skin is fixed t bone. Scarring of the face ithout distortion or ectropion.
Mucosae.	Erosions inner surfaces of lips nd under tongue or far back at sides. Papules on the dorsum fa back. The extragenital chancre or scar (seen but not suspected) Bismuth line	Hatching of lips. Scars nd rhagades ngles of mouth Nasal septum per forations. Early anterior palatal perforation. Leukoplakia at commissures. Tremors nd indurations in the tongue. Scarring of tongue nd fauces.
Teeth and tonsils.	Dental condition ith reference to treatment Pyor rhea, devitalized teeth, tonsillar lesions, especially erosions.	Focal infection possibilities.
Palms and soles.	Flat papules, pink t dark red, ith collarettes of scale. Often palpable. May be merely pink spots.	Circinat or gyrat groups of papules or lines of infiltration bordering reddened reas of thinning Paronychial and nail changes. Fusiform ellings.
Anus and genitalia.	Size and condition of vaginal introitus. Chancre and chancre scar (avoid phy mosis) Vaginal discharge Induration of intra-urethral chancre (palpate in long axis). Condyloma or mucous erosion disguised "hemor rhoid Condyloma or moist papule hidden in fold, especially gluteal Cervical chancre or erosions in women. Localized lymphangitis of penis ("pipestem") Mucous erosions and ringed lesions, posterior surface of s rotum.	Chancre scar Nodules in testis or epididymis. Odor of urine (incontinence) Hy drocele in children Fistula-n-ano. Stricture (rectal)

Fig 16.—Continued

Body Region	Early Syphilis	Late Syphilis
Lymphatic system.	Unilateral satellite adenopathy of extragenital chancre Submammary nodes. Visible cervical and post auricular adenopathy Palpable inguinal and epitrochlear nodes usually recognized Palpable spleen.	Gummatous lymphangitis (leg) Gumma of the lymph nodes (usually mistaken for tuberculosis) Palpable spleen often overlooked.
Skeletal system.	Painful spots over bones, especially skull and tibia Periosteal lesions, doughy deep, or superficial (make deep pressure or pinch firmly)	Floating patella (fluid in knee). Lateral play or hypermobility of joint (early Charcot) Stiff back (have patient stoop) Comparison of symmetrical joints. Juxta-articular nodules. Flattening of nasal bridge Minor destructive scarring ala nasi. Localized nontender exostoses, fusiform thickenings and irregularities of long bones, especially tibia. Thickening of inner third of clavicle and sternoclavicular joint. Costochondral and sternal thickening, edema, tenderness. Bumps on the skull. Condition of fontanelles.
Liver and spleen.	Slight jaundice Palpable enlargement (one or both often overlooked)	Palpable enlargement. Nodules and tumors. Abdominal fluid. Jaundice Compensatory venous enlargement.
Cardiovascular	Congenital and nonsyphilitic valvular lesions.	Supraclavicular and cervical pulsation. The early accentuation of A2 with slight rise in blood pressure and slight enlargement of heart Widened aortic dulness The aortic systolic and diastolic murmurs (heard but minimized or ignored) Markedly unequal blood pressure in the two arms Slight signs of decompensation (breathlessness, reduced exercise capacity slight edema of ankles) Early upper abdominal aneurysms (popliteal, etc) Venous ectasis (see prenatal syphilis)

compare the size of individual bones with the frame as a whole and to recognize the heavy clavicle of the prenatal infection as a suspicion-arouser Double swollen knees should not be put in casts without Wassermann testing and swollen joints, particularly knees should never be aspirated, until the pupils are examined.

Fig. 16.—*Continued.*

Body Region.	*Early Syphilis.*	*Late Syphilis.*
Nervous system.	Transient pupillary inequalities. Early seventh nerve rolings. Nystagmus, tinnitus, unilateral deafness (N viii)	Pupillary inequality due to unilateral lighting or congenital (not pathologic). Adie spastic pupillary syndrome Posterior synechia with fixation. Slight extraocular muscle weakness or paralysis. Nystagmus. Slight ptosis. Corneal opacities. Slight residua of hemiplegia (motor function) N viii. Abdominal and cremaster reflexes. Hand writing and composition tests (have the patient write a one-page letter). Sensory changes on the face Muscle atrophy and twitching

In the examination of the nervous system it should not be concluded that fixed pupils are necessarily Argyll Robertson. In a survey of syphilis in rail road men, 65 per cent of those who had the disease had pupillary signs of it entirely unrecognized though their eyes had been repeatedly examined by specially trained examiners for years The trouble was, that emphasis was all on color vision and visual acuity We have even had as a patient a railroad eye examiner who had grossly unequal Argyll Robertson pupils and did not know it.

In testing reflexes it is important to estimate the general tone of the reflex mechanism and never to call a reflex totally absent unless it does not respond to reinforcement. A hypotonia can be judged only in the light of all the reflexes and a uniform diminution. Again some patients in a state of high nervous tension, manage consciously or unconsciously to "hold" the reflex so that it may appear to be absent or diminished A hand on the contracting muscle and repeated reassurance may bring out the reflex after a few minutes effort. The Achilles reflex, in our experience, can be reliably and convincingly obtained only in the kneeling patient and the attitude should be comfortable for it can be completely veiled by a strained attitude. The cremasteric and umbilical reflexes should never be omitted and one writer on syphilis has even maintained that absence of these two reflexes in a person with a history of old syphilis justifies lumbar puncture In doing pin tests for pain sensation, the patient should be watched to see that he is not responding to differing degrees of pressure rather than to actual pain sensations in calling out "sharp" or "dull." Patients should, moreover be asked if they have been practicing such a test as the Romberg for many of them do The normals of the bone fork in testing vibration sense must be learned by experience. In testing for anesthesia, the circumanal region should be remembered If cutaneous lesions are present the center should be compared with the periphery before making a a diagnosis of neurosyphilis. We have seen a patient presented before a national society in whom failure to do this test and to feel the ulnar nerve, humiliated the presenter by his failure to recognize leprosy with a positive Wassermann reaction by simple neurological signs

CHAPTER III

THE FUNDAMENTAL DIAGNOSTIC TESTS IDENTIFICATION OF SPIROCHAETA PALLIDA

The Darkfield Examination

The necessity for the use of the darkfield in the early diagnosis of syphilis arises, as has been previously intimated in the characteristics of the organism itself The exceptional difficulty in staining it and the fact that its living characteristics rather than its dead form constitute the essence of its differential identification make observation of it in the living state a practical necessity for diagnosis For more than a decade therefore, with little regard for the practical considerations in the case syphilologists and public health officers have been urging on the medical student and the practicing physician the systematic use of the darkfield in the office for the identification of the casually-entering patient with early active syphilis. Only the experience of teaching darkfield technic to medical students has convinced us that the use of the darkfield as an instrument for the early diagnosis of syphilis has theoretical rather than practical value in the movement against the disease as a public health problem so long as the utilization of the procedure is left to the initiative and resources of the practicing physician. The necessity for special equipment in the form of sub- or supra-stage darkfield condenser or cardioid condenser which is of relatively little use in other fields of work the necessity for technical training, which can hardly be less than two weeks and which is readily forgotten or never given in the crowded regimen of the medical schools, make the examination of secretions by the darkfield an affair for laboratories, clinic centers and specialists. Darkfield examination can be developed by public health authorities into a centralized procedure like the identification and culture of the diphtheria bacillus That even laboratories and individuals claiming to make diagnosis of syphilis by the darkfield examination require supervision, is evident from complaints with reference to the work of commercial laboratories and the experiences of syphilis clinics which receive diagnoses made in this way by outside sources For this reason, a consideration of the darkfield examination in the diagnosis of syphilis is here given in detail for the benefit of the specialist, would-be specialist or physician with a special interest, while the course which the general practitioner is advised to pursue in securing early diagnosis of early lesions is separately outlined

Let it not be imagined that these remarks relative to the limited availability of the darkfield for the practitioner in any way affect the supreme importance of this form of identification of the organism for the diagnosis of syphilis at the present day Little short of a miracle will be either the serological test or the staining technic which can replace the darkfield procedure in identification of the *Spirochaeta pallida*. Previous optimism, based on hopes inspired by the skill and versatility of serological friends, has been rudely shaken in this particular by the expressed opinion, after years of effort, that it is improbable that any form of test of the secretion or serum from the infectious early sore can be made simple enough for ordinary office and perhaps even completely satisfactory laboratory use.

In 1905, when Schaudinn identified the *Spirochaeta pallida*, no satisfactory darkfield equipment existed. E. Hoffmann had used the Zeiss dark chamber in a search for the organism of

syphilis in 1904, without success, and nothing of the sort we know today was available until Reichert of Vienna demonstrated the organism with the Reichert substage condenser in 1906 (Ivory). The darkfield itself is, of course, a modification of the so-called ultramicroscope devised by Siedentopf and Zsigmondy for the study of the physical constitution of colloidal solutions. The principle employed is a surprisingly simple one: essentially that of the mot or dust particle visible in a sunbeam. Thus, in side or lateral illumination against a dark background, refractile particles stand out brightly defined in the transverse illumination. In the darkfield microscope the light from a powerful source of illumination is reflected upward by the substage mirror as in the ordinary microscope, and then thrown horizontally across the field at the level of the slide containing the object, so that the observer, looking down upon it, sees the specimen illuminated by horizontal rays comparable to those of the sunbeam in the darkened room. Direct rays are cut off by an opaque disk in the center of the condenser. The object in the microscopical field then stands out in contrast to the dark occluding disk background below it with remarkable brilliancy.

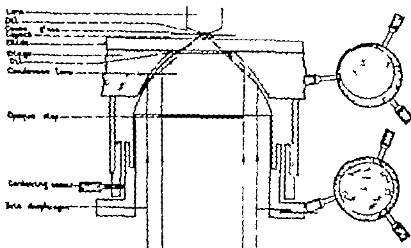


Fig. 17.—Schematic section of the microscope through stage, central aperture and oil immersion lens, showing the substage darkfield condenser in place and a specimen ready for examination, with immersion oil above and below the slide. To the right are two small schematic drawings of the condenser face by darkfield illumination, as seen through the low power of the microscope before the slide containing the specimen is in place. In the upper sketch the condenser is not properly centered, and the etched circle is eccentric to the margin of the field. In the lower sketch the condenser has been properly centered by the knurled set-screws, and the etched circle appears concentric with the margin of the field. Careful centering is important to proper illumination and definition.

Darkfield Equipment.—The improvisation of darkfield equipment under ordinary office conditions was described by Coffin in 1920 and further endorsed by Light in 1930.

According to Coffin, a piece of black paper the size and shape of a quarter pasted on the center of the lower convex surface of the Abbé condenser of the ordinary microscope, will make a darkfield apparatus for examination of the *Spirochaeta pallida*. The high, dry (4 mm.) objective is used and the light regulated with the lower shutter of the condenser. Light points out the desirability of the funnel stop and oil immersion lens mentioned later. A 75- to 100-watt lamp enclosed to prevent glare can be used to supply light to the reflecting mirror of the microscope. Good darkfield work can be done in the writer's experience with the ordinary Welsbach gas mantle, properly screened, and it is even possible to see spirochetes with the aid of a good Argand or student-lamp kerosene burner. We personally still cling to the small arc lamp in spite of its sputter and constant need of adjustment as the most intense and satisfying source of illumination we have used.

Darkfield Condensers.—Three types of darkfield condenser are in use at the present time The first is the flat-table type placed on top of the microscope stage with the darkfield condenser in the opening usually occupied by the Abbé substage condenser The second is the paraboloid substage condenser shown in Fig 17 The third and most recent development is the cardioid or hemispherical condenser Whatever type of condenser is employed, the devices for centering it must be thoroughly understood; it should be possible t focus the condenser to some extent to accommodat t the thickness of an overthin slide by up-and-down adjustment nd there should be a diaphragm below the condenser for regulating the amount of light admitted.

The one-tw lfth oil immersion lens is much superior to the dry lens for darkfield work but requires funnel stop to be inserted int the casing of the objective above the len system to cut dow the normal perture If this stop is not used the field is obscured by a glare through which nothing can be seen.

It is not intended to make the use of the darkfield ppear unduly discouraging to anyone who desires t take the necessary time t master it. From the interstices between the gums and the teeth any amateur can obtain multitudes of spirochetes for examination and can practice himself thoroughly on the details of the microscopical technic. Familiarity with the *Spirochaeta pallida* can be obtained only by seeing the organism itself and differentiating it from the types which it resembles. So far as the commoner contaminants of genital lesions are concerned, the knowledge is readily acquired. It is in dealing ith lesions on the mucous membranes that the possibilities of error become so great that none but the really experienced should undertake final nd differential diagnosis.

Setting Up th Equipment.—It is desirable in general in clinic and laboratory practice to maintain an instrument constantly set up for darkfield work, if the most satisfactory conditions are t be obtained. Information on satisf ctory microscopic units completely and permanently set up and requiring little or no adjustment can be obtained from optical manufacturers. On the other hand, it is entirely possible to take dow and set up equipment with each examination The centering of the darkfield condenser is an important part of the technic. On the face of each darkfield condenser bove the black disk, is ground circle (Fig. 17) slightly smaller than that represented by the low-power field of the microscope. When the condenser is inserted in it p oper place this circle is to be exactly concentric with the edge of the low-power field. The ad justment is made by looking through the low-power ocular and objective t the face of the condenser hich should be illuminated by the light reflected from the mirror below precisely as for darkfield ork. The condenser is then moved about by hand or by set-screws in the substage or by levers in the cardioid condenser until the bright circle is exactly concentric with the black margin of the field. The illumination is then adjusted by shifting the mirror below the stage and by moving the source of illumination nearer and farther (unless it has been set up at an optimum distance) until the circle is equally bright in all parts of its circumference. The condenser may then be moved up and down until the field has reached its smallest and brightest and the instrument is then focused and ready for use

Slides and Coverglasses.—For the most satisfactory operation, both the slides and the coverglasses used in darkfield ork should be sorted from stock by measuring with micrometer caliper only those of thickness specified by the manufacturer of the darkfield equipment being used in the ork. If the slide is too thick, the light comes to focus below the object on the surface of the slide and no satisfactory correction is possible. If the slide is too thin, Harrison points out that it is possible, by focusing the condenser t bring the light t focus upon the object thus obtaining satisfactory illumination. In the use of the oil immersion lens drop of im mersion oil is placed on the face of the darkfield condenser the slide containing the specimen is then laid on it ith an even contact of the oil between the two surfaces and entirely free from bubbles. A drop of immersion oil is then placed on the surface of the coverslip and the oil im mersion lens employed as usual. It is essential that slides and coverglasses shall be absolutel clean, free from scratches and defects. Casselman quotes Stitt as recommending paste of Bon Ami and water smeared over the slides and coverglasses, hich are then stored with the powder dry over them. Before use they should be polished, washed and dried.

Additional items which should be at hand before darkfield examination is begun include crystal-clear immersion oil, one pair of absolutely perfect rubber gloves, one small scalpel for scraping lesions, several long, thin capillary tubes with cotton plugs at the larger end for col lecting specimens from surfaces hard to reach several gauze sponges and supply of sterile phys ologic salt solution.

It should be emphasized that the handling of darkfield material and of instruments and equipment in use in the work is potentially dangerous. A

thorough alertness and awareness of every movement and the use of perfect rubber gloves in cleaning up equipment as well as in obtaining the specimens is an essential precaution against accident. All accidents moreover must be regarded as serious and the question of prophylaxis instantly considered (see p. 1227).

IMMEDIATE DARKFIELD EXAMINATION

Obtaining the Specimen.—It is extremely important to select for darkfield study lesions which are as young as possible, as nearly untreated as possible and as clean and free from detritus and secondary infection as possible. This triumvirate of requirements is seldom enough met in actual practice and, in fact, should be made the text of a systematic educational campaign among physicians and laity. Old lesions contain relatively fewer organisms because of the destructive effect of the local tissue reaction; treated lesions often have their surface organisms completely destroyed by escharotic and cauterant applications, and dirty lesions usually contain the *Spirochaeta refringens* which to the inexperienced is confusible with *Spirochaeta pallida*. It is for the purpose of removing mechanically the necrotic tissue favorable to the growth of the former that thorough cleaning of the lesion with scalpel, dry gauze and salt solution (Hoffmann also advises in some cases the use of alcohol to promote the flow of serum) is essential. Surface spirochetes obtained from pellicle, crust or detritus are always untrustworthy. The organism of syphilis is found in the serum from the deeper layers of the lesion.

Mouth and Throat Lesions.—The examination of lesions about the mouth and throat must be surrounded with special precautions and an expert should pass on all such specimens on account of the ease of confusion of the *Spirochaeta pallida* with mouth organisms. Whenever possible specimens from these regions should be obtained by aspiration of the bases of the lesions or by dissection of a small piece (Hoffmann) in the case of the tonsil, after thorough cleansing. Large cotton pledgets may be used to keep saliva and contaminating solutions away (Harrison).

Mahoney and Bryant (1934) found 40 per cent of nonsyphilitic tonsils to contain a form of spirochete, probably *T. macrodentium*, almost indistinguishable from *T. pallidum*—an indication of the unreliability of darkfield diagnosis in tonsillar lesions.

Gumma.—Darkfield examination of late gummatous lesions for syphilis is a futile procedure in the overwhelming majority of cases, for the *Spirochaeta pallida* is seldom present in sufficient numbers to be demonstrable by this method.

Satisfactory Specimen.—While a few blood cells are desirable in the darkfield serum, a marked visible contamination with blood renders the specimen almost useless. On surface lesions, if blood appears it may be blotted off and within a few moments enough clear serum will exude. This is collected by touching the surface of the coverglass to the lesion, a droplet 2 or 3 mm. in diameter being of sufficient size. It is essential that the film be thin, but not so thin as to dry rapidly. Once a good clean specimen of serum is obtained with perhaps 5 to 15 red blood cells to the oil immersion field, systematic alert and intensive searching should be begun and continued for fifteen minutes as an absolute minimum. A better plan is to search repeatedly but for shorter intervals over several days, two specimens being taken each day provided the lesion is large enough not to be ablated by this procedure.

Fig 18.

SUMMARY OF DARKFIELD TECHNIC

1. *Have at hand* rubber glo es (no pinholes) forceps; dry gauze; scalpel, not too sharp for scraping; immersion oil; slides nd 00 cover-glasses in alcohol. Great care must be taken t remov all the reagent from slides nd covers.
2. Clean t 00 cover-glasses nd t slides ith ter and 75 per ent. lcohol
3. Put on rubber gloves
4. Be sure the darkfield lamp is working and the darkfield i centered.
5. Have the patient lie down if possible He may f int.
6. Select the cleanest nd firmest based lesion vailable.
7. Pinch fairly firmly bet een the left thumb and index-finger and rub off exudat ith dry gauze until base is clean and bleeds slightly hen pressure is released. If the lesion is dry remov crust ith scalpel and scrape lightly
8. Release nd make pressure on lesion several times wipe off blood, nd lightly touch the cover-glass to the clear serum. The drop on the glass should be bout 3 mm in diameter Place t once on slide nd press int close cont ct with clea instrument.
9. Dry lesions, phymotic lesions, old lesions (over tw eeks) sometimes yield rich fields by putting constricting rubber band around penis for from ten to fifteen minutes until there is definite edema
10. Place drop of immersion oil on darkfield condenser face and place microscope slide on stage, cover-glass up. *The oil below the slide must make even contact ithout bubbles.*
11. Place another drop of immersion oil on cover-glass and examine specimen with oil immersion objective in the usual way
12. Make second, nd even four or fi preparations.
13. Search the best specimens for from seven to ten minutes each.
14. Clea up the instrument soon you are through using it.

Fig 19

CAUSES OF TROUBLE IN DARKFIELD WORK

1. Poor equipment, or equipment not adapted t the instrument with which it is used.
2. Dirty cover slips, scratched slides, air bubbles which fill the field with glare. Bubbles in the immersion oil may cause trouble
3. Poor lighting. Not less tha 75 to 100 tt tungsten bulb is desirable
4. Poor centering of condenser Impossible to get even illumination. Follow maker directions exactly
5. Taking down and setting p equipment. If much ork is done separat microscope should be kept set up for this purpose.
6. Forgetting to put funnel stop in oil objective. A diffuse glare result
7. Not getting th light from the enter or brightest point of the lamp, makes the field uneven, or dim, or gives refraction rings (halos) around the objects. T correct, shift mirror about until the best illumination is secured This must usually be done for each specimen or t each sitting
8. Too much oil on condenser face. Floods the condenser nd ma spoil equipment by getting oil under nd loosening opaque stop or disk.
9. A glare of light bove the stage from indow room illumination, et A darkfield orks t best dvantage in dark room or box
10. Too thick or thin cover-glasses or slides. Hard t illuminate. Adjustable
11. Too much serum. Makes field seem afloat, hard to focus, very "jiggly
12. Too much blood. C see little except rouleaux of blood-corpuscles
13. *Currents in the field.* Due to dirty cover-glasses or slides pressure of objective on cover-glass too much serum, hich ppears t cover-glass edge drying, due to heat, draft, etc oil hich ha run over the edge of the cover-glass (too much oil or orking too near edge of cover)
14. A dirty specimen. Swarms ith miniature suns (pus cells), fibrin, and dventitious cocci and other organisms

A maxim of J H.S s preceptor Professor Wile gives the gist of the matter "Look till you find them." The more determined the worker the higher his ultimate score Once an experienced user of the darkfield has the intuitive

sense that he ought to find the organism in the lesions he is examining, he will spend an hour on several good specimens The irksomeness of the repetition is lost in the glory of the find One of our assistants succeeded in establishing the identity of a treated lesion in the face of every odd by finding the *Spirochaeta pallida* on the twenty-first darkfield search on the sixth day after the lesion was first seen and while the Wassermann test by one of the older technics was still negative

It is seldom given a fresh untreated lesion that two or three typical *Spirochaeta pallida* are not found in the first field and from this average their number may vary from 12 to 15 in each oil immersion field to one or two in an entire specimen When the organisms are so few the trustworthiness of the find must be critically considered and expert opinion on the morphology of the organism should be secured

Obtaining Specimens from "Dry" and Previously Negative Lesions.—If the initial search is a failure hope should by no means be given up "Dry" lesions from which it is difficult to obtain serum may be subjected to suction Chambers devised a suction device consisting of a syringe connected with catheter tubing to the barrel of a second syringe Phimotic lesions and old lesions (over two weeks) sometimes yield rich fields by putting constricting rubber bands around the penis for ten to fifteen minutes until there is a definite edema. Igersky (1034) obtains deep serum by cauterizing lesion base or edge with the platinum loop In serial examinations, saline soakings or gentle cleansing of the lesion will often bring the organism to the surface E. Hoffmann also employed the excision of a small piece of tissue or the making of a transverse vertical incision through the upper layers of the lesion. Chambers has applied the Krajian modification of the Dieterle method of section staining to the examination of small slices from the edge of the chancre (see stains)

The technic of aspiration of the base of old or even actually healed lesions practically identical with that used for the aspiration of lymph nodes (see below) often yields satisfactory specimens A small needle passed horizontally into the base of the lesion (not vertically) is employed with an aspirating syringe

Inaccessible and Unusual Lesions.—The *Spirochaeta pallida* may be obtained from cutaneous lesions on the dry surface of the body occasionally by careful aspiration of the individual macular lesions of a roseola and by scraping the bases of syphilitic pemphigus bullae on the palms and soles of syphilitic infants Hoffmann aspirates the palpable border of lesions on the foreskin which are causing phimosis in order to do away with the necessity of retracting the foreskin The aspiration is made directly through the skin of the prepuce The *Spirochaeta pallida* may be obtained not only from cervical erosions in the woman but from the secretions of the cervical canal. Long capillary tubes should be employed. Difficultly accessible deep lesions may be aspirated with the so-called "tonsil anesthetizing needle" with its Luer extension.

Lymph Node Aspiration.—Schaudinn and Hoffmann in their original communications describe the extremely valuable method of obtaining lymph node juices from adjacent enlarged nodes by syringe and needle aspirations To this technic has been added by Schultz and Sutton that of injecting a drop or two of physiologic saline solution and reaspirating it from the gland tissue or of distilled water used for the same purpose the purpose being to secure a certain amount of lysis of red blood cells. The great advantage of

such a method in dealing with lesions on contaminated surfaces such as the mucosae is in the fact that no pseudopallida organism has ever been recognized in the lymph nodes, so that the demonstration of spirochetes in lymph node juices is tantamount to a diagnosis of syphilis, and has medicolegal value. The technic of examination used at the University of Pennsylvania clinic is as follows:

1. Use rubber gloves.

2. A 3 cc. Sana-lok syringe, a 1½ inch 21 gauge needle, sterile saline and an alcohol sponge are needed. The needle and syringe are sterilized by boiling, the syringe is rinsed out with a small amount of saline, which is completely expelled and the needle is then attached.

3. The skin over the enlarged lymph node is rubbed vigorously with 70 per cent alcohol, and this is allowed to dry. The lymph node is identified and firmly held by the left hand between the thumb on one side and the index finger and ring finger on the other along its long axis. The Sana-lok syringe is held in the right hand with plunger in the "expelled" position. The needle is introduced along the long axis of the lymph node, about ½ inch to the right, and is then plunged into the body of the lymph node. One can be sure that the needle is in the lymph node by manipulating the syringe with the right hand and noting movement of the lymph node.

4. Immediately after penetration of the lymph node suction is employed by withdrawing the plunger of the syringe and the needle is rapidly plunged in various directions throughout the lymph node now firmly held by the left hand. This operation can be completed within 10 seconds.

5. The material obtained is usually milky and should not be too blood tinged. As a rule, enough fluid is obtained for 3 or 4 preparations, which can be examined by darkfield. A satisfactory specimen should contain at least 10 and *preferably more lymphocytes per high power field*.

While the number of organisms may be small, the identification of *Spirochaeta pallida* in the lymph nodes was accomplished by this method in nineteen of twenty cases of early syphilis.

Scrapings from the Umbilical Cord.—Ingraham (1935) used a 3-inch piece of fresh cord (portion nearest the child) kept in moist bottle and examined within eight hours using the middle inch splitting the single vein and scraping the lining after removing blood. Two preparations, ½ hour search. Often positive with negative cord blood serology.

Darkfield Examination of Pus.—Friedman (1939) at the University of Pennsylvania under Beerman's supervision developed a capillary tube method with centrifugation at 1000 revolutions which was successfully applied to the examination of urethral gonorrheal pus with three positives in forty cases and positives in other bloody and purulent material. The organisms are found at the junction of the sediment and supernatant serum.

Differentiation of the Spirochaeta Pallida and Artefacts as Seen in Darkfield.—The description of the living *Spirochaeta pallida*, verbal accounts of its differential morphology should not leave too unfavorable impression of the difficulties encountered in identifying the organism. None the less, there can be no denying that experience is essential in necrotic lesions, sometimes even after thorough cleaning, in lesions within the mouth and throat; and in foul cond lomas. Of the mouth spirochetes, *Spirochaeta microdentium*, while quite regular in shape, is only about half as long and half as thick as the *Spirochaeta pallida*, and consequently appears more minute. It may, however, in the longer forms, be almost indistinguishable except by its deep bluish staining with Giemsa. The coarse, large, very actively motile spirochete of Vincent's angina cannot possibly be confused with the *Spirochaeta pallida*. The spiral of the *Spirochaeta*

refringens is coarser with fewer less rigid and more regular turns. The movements are more rapid than those of *Spirochaeta pallida* and it does not keep its shape so well. The habitat of the *Spirochaeta refringens* indicates the means of practically eliminating it from the differential diagnosis by thorough cleansing of the lesion and the obtaining of organisms only from exuded serum. While in lesions within the mouth, surface material must be passed on by an expert, lesions on the lips seem less contaminated with adventitious saprophytes.

Once the student has clearly seen the highly distinctive characteristics of the *Spirochaeta pallida* he rapidly gains facility and trustworthiness in diagnosis. The spiral is of a peculiar brilliancy rigidity and regularity which is retained whether the organism is in motion or at rest and which suggests more than anything else as seen in the darkfield the rigidity of a steel shaving, and the brilliancy of a lamp filament. While the organism drifts with currents in the field its intrinsic movements are the slowest of all the spirochetes with which it is likely to be confused Other spirochetes are more *translucent, they collapse distort while in motion and squeeze into threads* between apposed objects in the field—but the *Spirochaeta pallida* "keeps its twist. It is, in the phrase so often used by Warthin, the organism "with waxed moustaches par excellence

Certain artefacts in the darkfield have caused inexperienced observers a good deal of difficulty at times. The commonest of these is the fibrin spiral, a waving bit of fibrin, often crinkled and attached at one end, which lacks the sharp clear-cut, spiral contour It wrinkles and is much finer and less refractile than the *Spirochaeta pallida*. Its attachment to the cover or slide can be readily detected by pressing lightly with an instrument point on the cover while the field is being watched. A second artefact, especially important in research work, is that described by Eberson as forming from red blood cells the carbon dioxide tension of the serum changes. We have occasionally seen these corpuscular rosettes in human blood serum and while no trained observer should misinterpret them, they may at times confuse the beginner into believing they represent clumped spirochetes

DEFERRED DARKFIELD EXAMINATION

Deferred darkfield examination by which is meant the examination at periods ranging from twenty four hours to several days after their collection of specimens of serum from suspected syphilitic lesions, is a procedure practically unknown in this country but one with many possibilities of development. It is not proposed that this technic of making an early darkfield diagnosis shall be regarded as superior to the direct examination of the patient. It has none the less a sufficiently high degree of applicability to have led the British Venereal Disease Service to adopt it as a practical device and a number of American State Laboratories, including those of New York and Pennsylvania, have made available mailing kits conforming essentially to the specifications of Mahoney and Bryant of the United States Public Health Service (Fig. 20)

Riehl, in 1919 and coincidently Scherreschewsky using glass capillary pipettes sealed by fusing in flame, first demonstrated the practicability of this method. Riehl found recognizable *Spirochaeta pallida* as long as fourteen days after collection W. H. Stokes and Leroy Ewing, in 1925, described an outfit for physicians to collect serum for darkfield examination. Mahoney and Bryant used fine straight capillary pipettes about 8 cm. in length and of constant bore. Harrison (1934) found *Sp. pallida* motile after eighty-four days in capillary tubes after having been shipped across the Atlantic four times.

The serum is collected from lesions as previously described, and the fine glass tubes (Fig 20) are filled by capillary action The ends of the tubes are then closed by pressing them into the soft paraffine vaseline mixture in the

small bottle for a distance of about 1 cm Serum containing *Spirochaeta pallida* secured both from experimental animals and from human cases of primary syphilis when thus sealed appears to support the organism in a viable and

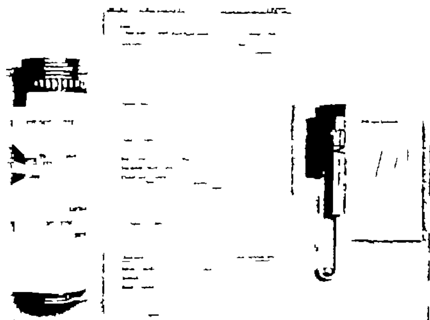


Fig 20 —The mailing kit for collecting material for darkfield examination, supplied to practitioners by the New York Stat Department of Health It consist of glass capillary tubes corked test-tube container small bottle of wax for sealing the capillary tubes mailing case nd instructions



Fig. 21 —*Spirochaeta pallida* from chancre Darkfield × 1000 (Collection of Dr Noguchi.)

entirely recognizable state for a considerable period of time While refrigerator storage yielded the best preparations good results were obtained in specimen kept at room temperature. Incubator specimens rapidly became unsatisfactory Motility progressively declined in twenty four to forty-eight hour

specimens but seemed to be confined chiefly to the larger motions, as bending and progression Distinctly motile forms were observed however at ninety six and one hundred and twenty hours and even longer Entirely recognizable forms were observed in one ice-box preparation thirteen days after collection



Fig. 11.—*Treponema microdentium* from the mouth Darkfield, × 1000. (Collection of Dr Noguchi.)

of the specimen Mahoney and Bryant give it as their opinion that the liability to error or faulty diagnosis does not seem to be great when the work is in the hands of an experienced microscopist, skilled in darkfield work. Modern equipment greatly facilitates the work.



Fig. 12.—*Treponema macrodentium* from the mouth. Appearance of young forms Darkfield × 1000 (Collection of Dr Noguchi)

The Paramount Value of Darkfield Diagnosis.—The most urgent need in the utilization of the darkfield in early diagnosis is an appreciation by physicians of its tremendous importance While this will be reemphasized in the clinical chapters, it is not out of place here to point out that while blood for a

serological test should be taken at the first visit, the use of the positive blood test for the identification of the syphilitic primary lesion on which with little trouble, an earlier darkfield examination might be obtained is unpardonable. It perpetuates an infectious focus and it loses the patient from 25 to 35 per



Fig. 24.—*Treponema genitalis* from smegma. Darkfield × 1000 (Collection of Dr. Noguchi.)

cent of his chance for complete and lasting cure. An untreated lesion is extremely important though not absolutely indispensable to a satisfactory examination. All educational campaigns and antivenereal movements should stress this fact and fight the tendency to self medication, drugstore prescrib-



Fig. 25.—*Spironema refringens* (culture). Darkfield, × 1000. (Collection of Dr. Noguchi.)

ing and oldtime casual doctoring (indiscriminate cautery, dusting powders and so forth) which defeat effective darkfield work.

The Securing of Darkfield Examination in Ordinary Practice.—Every practicing physician should be in touch with a hospital pathologist or a venereological specialist or a diagnostic laboratory of whose equipment and

expertness he is personally sure From them he should obtain cooperation for darkfield examination which he may not himself be equipped to perform The larger city health authorities are establishing darkfield stations in connection with other local laboratory facilities and clinics The physician should



Fig. 26.—*Treponema calligyrum* from smegma Darkfield × 1000 (Collection of Dr Noguchi.)

if possible accompany the patient to the specialist or send someone with him who will see that he gets there. No deferred darkfield examination can take the place of the personal conference between physician and specialist both as to diagnosis and treatment, or the value of the specialist's clinical examination



Fig. 27 —*Treponema cuniculi* from venereal lesion of the rabbit Darkfield × 1000 (Collection of Dr Noguchi)

tion in addition to the darkfield Node and lesion aspirations can in the present state of knowledge be secured only in this way The highest efficiency in the darkfield examination occurs within the first two weeks of the primary lesion and an even shorter period for more superficial lesions The shorter the

duration of the lesion prior to examination (i e., the fresher) the more significant a negative finding but no negative darkfield examination in and of itself even if repeated fully eliminates syphilis from the diagnosis All negative darkfield examinations should be followed by serological tests and serological follow-up as described on page 520

Stains and Tissue Methods for Identifying Spirochaeta Pallida

Staining methods for *Spirochaeta pallida* have increased so in number and amplification in the past decade, and reported superiorities are so far unconfirmed that a bibliography of recent technics is offered. Their common but inevitable disadvantage is the lack of the living form and movement of the organism

For details of technic of the following methods see the second edition of this work

Noguchi-Tilden buffer solution method; The Fontana-Tribondeau and Fontana arsphenamine-silver method *Levaditi silver reduction method Warthin-Starry stain for section work*

Some additional methods and modifications for smears and tissues have been recently proposed as follows

Krajian, A. A.: Am. J Syph., 17 127 1933 Ono, K. Loes, 11:7 1934; Krajian, A. A. Arch Dermat. & Syph., 32:761 1935 Kline B S., Am J Clin. Path., 7:19 (Tech. Supp.) 1937 Steiner G J Lab. & Clin. Med., 23:093 and 315, 1937 Haire, R. D.: ibid., 23:1215, 1938 Garvin, T Am J Clin. Path Tech. Supp 2 144 1938 Ono, K. Acta Dermat., 31:60 1938 Kerr D A. Am. J Clin. Path., 8-63, 1938 Steiner G J Lab. & Clin. Med., 24:201 1939 Kniseley M. J ibid., 24 1500 1939 Krajian, A. A : Am. J Syph. Gonor & Ven. Dis., 23:317 1939 Nagle N and Graul, J J Lab. & Clin Med., 25:980, 1940

CHAPTER IV

SEROLOGICAL TESTS ON BLOOD AND SPINAL FLUID

The Mechanism of Serological Tests. The life history of serodiagnostic procedure in modern syphilology like the history of the discovery of the *Spirochaeta pallida* contains the unmistakable hallmarks of drama.

Bordet, in 1898 first clearly described serum hemolysis in the test tube. The half century since elapsed has seen the struggle between clinical and laboratory interpretation, the battle of clinical syphilologist and laboratory serologist for supremacy; the war between specificity and sensitivity in the tests themselves; the slow and difficult development of control in the older test, whole lifetimes of labor bestowed upon the perfection of the complement fixation procedure; and finally the rapid rise of flocculation methods with their lessened expense and increasing accuracy and the impending triumph of simplification in precipitation. The past ten years have been marked by international and of late especially American national comparison for purposes of standardization of a limited number of test and the development of mechanisms for the control of accuracy of laboratory performance. The nature of the syphilitic reagin, its presence in normal individuals its relation to the mechanisms of agglutination and antibody formation and its presence in normal individuals are under investigation. The positive serologic test has succeeded the negative as an object of challenge and investigation, and the biologic false positive, long regarded as a rarity has proven to be a significant factor in everyday diagnostic interpretation. Methods for the differentiation of biologically true and false positives are the chief immediate concern both of clinicians and serologists, today.

Fig. 28

MECHANISM OF THE WASSERMANN TEST

1. **Based upon the Bordet-Gengou phenomenon of fixation of complement.**
2. **Five distinct substances used, interacting in two groups, called the antigenic and the hemolytic systems.**
3. The hemolytic system is an indicator of what has happened in the antigenic system.
4. *The test may be performed on the blood-serum after removal of cells, on the spinal* fluid, extracts and secretions of syphilitic or other tissues, exudates and transudates.
5. **The five elements entering into the reactions are**

Complement, a chemical substance present in normal and pathologic blood in man and animals. It can be destroyed by heating to 56° C and when thus destroyed the serum is said to be "inactivated," and complement from another source must be added before the Wassermann reaction can be carried out.

Syphilitic amboceptor a substance which appears in the blood as a result of syphilitic infection, and which is not destroyed by heat. This element and complement form the reacting part of the syphilitic patient's serum.

Syphilitic antigen, extracted from syphilitic and certain other tissues and added to the serum for the purpose of binding the complement through the intermediation of the syphilitic amboceptor. The union between these three substances is indissoluble and when quantitatively carried out results in the "binding" or "fixation" of the complement, so that it cannot participate in the subsequent hemolytic indicator reaction.

Red blood-cells, obtained usually from sheep or man, washed and used quantitatively in a physiologic saline suspension. The lysis of these red blood-cells by their union with any unbound complement through the intermediation of the *hemolytic amboceptor* that indicates a "negative" Wassermann reaction.

Hemolytic amboceptor, which is obtained by immunizing a laboratory animal, usually a rabbit or dog, against the red blood-cells of sheep or man. When these red blood-cells are injected into the animal, the animal develops a specific hemolytic amboceptor which, combining with the normal complement of serum, produces hemolysis of the injected red blood-cells within the animal body. This reaction can be transferred to the test-tube by using the animal serum with a supply of the corresponding red blood-cells (4 to serve as an indicator for the presence of unfixed or unbound complement in the Wassermann reaction.

Both because it is historically the older procedure and because once its mechanism is clearly envisaged the strength and weaknesses of serological procedure in the diagnosis of syphilis become almost *ipso facto* understandable Figs. 28 and 29 first set forth the mechanism of the Wassermann test itself

All precipitation tests as now used are essentially equivalent to the antigenic system of the Wassermann reaction minus the complement with of course important technical modifications, the results being read direct. The

Fig 29

MECHANISM OF THE WASSERMANN TEST

The Antigenic System

1 *Complement* present in the patient's serum or if this has been inactivated, added in the form of *guinea-pig complement*
2. *Syphilitic amboceptor* also present in the patient's serum if the patient has syphilis, but *absent if he has not*
3. *Syphilitic antigen*, added to the serum in an amount proportional to the amount of complement known to be present, so that complete fixation will occur if the requisite amount of syphilitic amboceptor is present.

The mixture of these reagents is subjected to incubation or refrigeration, or both. If syphilitic amboceptor is present, the complement is fixed to the antigen, and the serum becomes incapable of reacting to the subsequent addition of the hemolytic indicator system. If syphilitic amboceptor is not present, the complement remains free and can enter into the next reaction, as soon as the hemolytic amboceptor and red blood-cells are added. The second system is, therefore an indicator of what has happened in the first.

The Hemolytic System

1 Hemolytic amboceptor in known amount, consisting of the serum of the immunized animal
2. Suspension of red blood-cells in an amount to correspond to the complement originally present and to the amount of hemolytic amboceptor added.

The mixture of the two systems is again incubated at body temperature

If the patient has syphilis, all the free complement will have been fixed by combination with his syphilitic amboceptor and the added antigen, and none will be available for the hemolysis

A Total Absence of Hemolysis Therefore Means Syphilis is Present.

If the patient does not have syphilis, all the complement will remain free or unfixed, for participation in the hemolytic indicator reaction as soon as the second group of reagents is added, and complete hemolysis of the red blood-cells will take place

Thus "Negative" Hemolysis Means Positive Wassermann and Positive Hemolysis Means Negative Wassermann.

The degree of hemolysis which occurs is to some extent a measure of the intensity of the Wassermann reaction. The more hemolysis the weaker the reaction. The more accurate method of making quantitative estimations of the degree of positiveness, however consists in varying amounts of reagent used, and especially of the fluid or serum which is being tested. Strongly positive sera produce complete inhibition of hemolysis in very small amounts.

Remember that the Wassermann Test is Not Infallible.
Positive Wassermann Tests, Like Negatives, May be False Technically or Biologically

physical precipitate produced in the positive serum by the mixing of antigen and syphilitic amboceptor is read by a variety of devices ranging from direct vision in the Kahn and Hinton tests, for example to various photometric procedures, as in the Vernes, and by the microscopical study of the precipitated aggregate as in the Kline test. One of Kline's diagrams here reproduced (Fig 30) visibly portrays the difference in complexity to say nothing of simplicity in materials required between the standard Wassermann proce-

WASSERMANN TEST
MATERIALS REQUIRED

SLIDE TEST
MATERIALS REQUIRED

Fig. 30 — An illustration of the simplicity of a precipitation test as compared with Wassermann from the standpoint of biological materials required. (Courtesy of Dr. R. S. Kline.)

Fig. 31

TOPICAL SUMMARY OF SEROLOGIC PROGRESS SINCE 1932

1. Better comprehension of immune body and syphilitic reagin relations.
2. Light on the specificity of tests for syphilis by the use of a spirochetal antigen (the Reiter and other antigens).
3. The presence of syphilitic reagin demonstrated in apparently nonsyphilitic human and animal blood.
4. Development of methods (Lund) for identifying minute amounts of syphilitic reagin. An investigative method.
5. Use of reagin titration in diagnosis and treatment.
6. Emphasis on quantitative serologic technics.
7. Recognition of zone reactions as sources of nonagreement in same serologic test.
8. Passing of the provocative procedure.
9. Continued controversy on contradictory and conflicting serologic result.
10. Testing of specificity and use of ultrasensitive procedures (screen, presumptive, exclusion and elimination tests) to exclude syphilis from effective diagnosis.
11. Increasing demonstration of the margin of error of the positive serologic reaction—expanding field of biologic false positives.
12. Development of procedures for differentiation of syphilitic from nonsyphilitic positives—verification tests.
13. Standardization of American serologic laboratory practice—approved tests, approval status based on extensive cross-checks of laboratory performance. Results of conferences. Approved methods of reporting.
14. Rivalry between newer simplifications and approved or standard tests.
15. Development of state laboratory systems. National possibilities.
16. Mass serologic testing and routine use of a case-uncovering mechanism.
17. The enactment and influence of blood-testing laws.
18. Definition of blood test and infectiousness relationships.
19. Relation between reagin content of the blood of mother and newborn child.
20. Declining clinical importance of seroresistance (fixed positive).
21. Initiation of research into the nature of the syphilitic reagin by chemical and physical serum fractionation methods.

dures and one of the simplest and most accurate of the precipitation technics Important recent efforts to simplify and make more available the reagents employed in standard complement fixation procedure include control of preparation by the originators of tests, and for example the Flosdorf Mudd cryochem process of drying frozen guinea pig serum for preservation of complement.

FACTORS IN SEROLOGICAL TEST PERFORMANCE AND INTERPRETATION

Laboratory Aspects.—The use of serological tests in the diagnosis of syphilis requires a partnership between serologist and clinician in which neither party should permit his native enthusiasms to blind him to the functions, duties and critical prerogatives of the other The interrelations involved can usually be made clearer by considering the two sides of the problem to some extent separately and combining the conclusions in a summary of the place of serological tests in medical examination

Rôle of Equipment and Reagents.—Certain elements are common to both complement fixation and precipitation technics but the former type because of the added complexity of a hemolytic system, inevitably involves the larger possibilities of error The first and most important item in the performance of serological tests is the antigen, which is common to both types.

Antigen.—The original antigen used in the Wassermann test was an aqueous extract of syphilitic fetal liver Within short time it was found that alcoholic extracts were more satisfactory that the use of tissue containing spirochetes as the source of the antigen was not necessary and that very satisfactory antigens could also be made from alcoholic extracts of human beef or guinea-pig heart from which the gross fat had been removed. The active principles of antigens are lipoidal in character The antigen is the foundation of each test procedure and the precise instructions of the originator of the method must be followed to the letter in preparing this basic reagent Even with considerable effort, antigens made in other laboratories than that of the originator may differ for reasons not as yet understood, and it may be necessary at times to secure the personal assistance of the deviser of the method in preparing the first batch of antigen. So critical is this issue in certain procedures, such as the Vernes, that the originators of the method have felt it necessary t place the manufacture of their antigen in the hands of responsible technician and t urge all users to procure their supply from headquarters or uthorised distributors. The complexity and difficulty of control of the original Wassermann procedure led to divergences in the preparation of different antigens almost as numerous as the proponents of individual systems. Antigens in general are prepared by soaking the selected minced tissue in 95 per cent alcohol for some eeks Various tissues differ markedly in their antigenic properties and even individual organs of the same anatomical type as, for instance beef heart, vary as prepared from different specimens The titration and standardization of antigen preparations and the bringing of individual fractions up t normal antigenic strength by cholesterinization is an important part of the ground ork of all serological laboratory procedure Wassermann technic, with its almost innumerable modifications, as distinguished up to within the past half decade by multiplicity of antigens, of hich the alcoholic extract of syphilitic liver of human, beef and guinea-pig heart formed one group the antigens standardized or increased in sensitiveness by the use of cholesterol constituted second group and the acetone insoluble fraction antigen, of which Noguchi' was the prototype, constituted third group Each of these types has somewhat different reactivity in the Wassermann procedure and may yield somewhat different results on the same serum. Multiplicity of antigens in the performance of serological tests was therefore virtually necessity in order to provide cross checks p thus the test itself on the results obtained ith given serum.

Kline and his coworkers, Levy Wellman and Lankelma, have been notable in this country for their efforts to free the essential antigenic substance of many impurities and contaminants and t ascertain if possible something of its chemical structure. Important publications have appeared (1937 1940, 1941 1942) Pangborn (1942) has isolated pure phospholipid cardiolipin, which is essential for the reactivity of beef-heart antigens in the serologic test for syphilis. The theory of antigen formation and action is discussed ith extensive bibliography by Weil Bacteriologic *Reviews*, 5 223, 1941 See also *Ratcliff* J Lab and Clin Med 27 729 March, 1942

With the perfection of precipitation tests on the one hand and the introduction of an antigen like the Kolmer in which the factors of control have been covered by an extremely elaborate investigation over a period of years the necessity for multiple antigen tests has declined and few antigens now receiving support from individual laboratorians will survive the demise of their inventors. There will remain, for a period of years perhaps, two or three standard antigens used in a quantitative procedure and controlled by precipitation as distinguished from complement fixation technic.

Complement.—Complement previously obtained from normal guinea pigs, was subject to considerable variations dependent on the frequency of bleeding, feeding of animals and so forth. These have been largely overcome and complement has been made available in almost standard form by the process of lyophilization. The manufacturers warn that the titer of lyophilized complement should always be compared with the titer of fresh complement before use. Kolmer Richter and Lynch (1938) regarded lyophile complement kept at 4 degrees to 10 degrees C satisfactory for complement fixation tests for syphilis for ten to thirteen months. Boerner Flosdorf and Lukens (1941) have stabilized vacuum-dried complement from large pools so that its potency may be extended to over three years.

Other Reagents.—All other reagents used in serological tests must be subject to constant check. Their titer must be carefully determined at intervals and in the manner prescribed by the originator of the procedure used. Salt solution must be accurately made up, the pH of the salt solution, the use of tap water as against distilled water the temperatures of room and reagent at the time of preparation and mixing, all requiring attention among the factors of control.

Care of Glassware.—This detail, especially with respect to the removal of all grease from the glass and test tubes is an important element in laboratory work with the serological tests and technicians who are careless on this point cannot be trusted. We have personally seen several near disasters and prolonged inaccuracy traced to this factor especially in small laboratories.

Fixation Temperature, in the Complement Fixation Procedures Especially.—Ice-box (Jacobsthal) and ice-bath (Duke) temperatures materially increase the sensitiveness of complement fixation reactions without increasing the risk of false positive results. It is important to point out, however that uneven cooling in a rack of tubes, for example, dependent on position in a refrigerator may lead to serious degrees of false positiveness in certain tests in a batch. The method of refrigeration, like that of incubation, requires, therefore, careful supervision. The time required for incubation and refrigeration in the complement fixation test is one of the most serious elements of delay and gives the more recently devised precipitation procedures a marked advantage in the form of prompter reports. The observations of Kline and Kahn on the temperature factor in precipitation reactions especially as affecting specificity are currently important.

Hemolytic System, Active or Inactive Serum.—Questions involving these details of technic are still too controversial for the average physician to concern himself with them. In this country the Craig (Army) and Kolmer systems use an inactivated serum, and the Noguchi system uses an active serum. British Medical Research Council system, No. 1 official for the British Venereal Disease Service, uses inactivated serum. The Hecht Weinberg system uses an active serum. The Army and Noguchi systems are antihuman, the Kolmer British Medical Research Council No. 1 use an antisheep system. The earlier reports in the case histories of this text were from tests performed by Sanford's system, employing an antihuman hemolytic system and an active serum. The system employed by Keidel and Moore at Johns Hopkins, on which many important publications have been based, uses an antisheep hemolytic system and an inactive serum.

Animals.—The condition of the animals used in complement fixation procedures is important. Too frequent bleeding alters the fragility of the red cells and Weyler has been able to demonstrate surprising variations in complement titer on guinea-pig blood by comparing the guinea-pigs which he used in London with those he used during the Second Serological Conference in Copenhagen, Denmark. It appears that feed may alter the characteristics of these biological reagents and accordingly one may expect variations in sensitivity and performance during summer compared with winter.

Collection of the Specimen.—Sticklers for exactitude may properly insist that blood be drawn from the patient before any ingestion of food for the day the theoretical ground for this stipulation being the possible excess of lipoid present in the blood after meals. The risk of false positives, in our experience, is not serious. But the point deserves consideration in ticklish cases. Craig and Nichols have shown that the ingestion of alcoholic liquors within twenty four hours before a complement fixation test may inhibit a positive reaction and render the serum negative to the Wassermann. In weak positive cases it is especially important to bear this fact in mind. Blood for serological tests must be aseptically drawn. Bacterial contamination of the blood specimen either through carelessness in drawing or through delay in testing a specimen markedly contaminated by improper shipment or storage is occasionally responsible for false positive results Craig points out, however that the degree of contamination and delay must be considerable so that this factor becomes operative only occasionally Stale sera are apt to be anticomplementary in the Kolmer test and are unsatisfactory for examination by technics using active serum or native complement. All specimens of blood for complement fixation tests should be handled under glass or cork seal since cotton fiber is said to produce changes leading to false positive results.

Wenger (1939) and Tulsky have called attention to the factors responsible for *hemolysis which causes the loss of many specimens whose examination is* delayed by mailing and so forth. Among these factors are distilled water in syringes, increased fragility and destruction of red cells by the use of force in ejecting blood from syringes (and possibly also in aspirating it from veins under marked suction)

Handling of the Specimen.—Much emphasis deserves to be laid on this point. There can be no question that even in the best laboratory practice *specimens are sometimes mislabeled, tubes are exchanged and erroneous* reports follow The practical details especially for the attention of nurses handling blood specimens, are given on pages 329 and 330

Anticomplementary Substances.—Unknown substances may be present or develop in serum on standing, which, because they destroy complement, produce false positive result (inhibition of hemolysis) in both serum and control Certain of these substances can be destroyed by heat but others cannot, and may make it impossible to perform Wassermann test on the serum thus affected. The occurrence of frequent anticomplementary reports in the work of laboratory is, in our experience evidence of a faulty technic and calls for investigation. The difficulty should be rare Flocks of anticomplementary reports usually appear when laboratory is testing out new method and we have heard it as the first objection offered to new system which was later accepted in its entirety without protest, when experience had done away with the technical difficulties

Technicians Technical Experience Serologists Interpretation.—The last ten years has seen a gradual recognition on the part of clinicians of the immense labor the constant vigilance, and the large element of experience which goes into the personal side of the performance of serological tests for syphilis. While the advent of precipitation procedure has unquestionably helped the situation materially it is a mistake to imagine that even the simplest of the precipitation procedures can be performed by any amateur anywhere, *at any time* without grave risk of error The clinician, compelled to interpret the results of laboratory tests by the touchstone of the clinical picture of the patient himself realizes perhaps even better than the serologist

how subject to revision and reinterpretation all statements particularly by the proponents of test procedures, must be held.

Just as animals in London differ from those in Copenhagen, antigens prepared in the originator laboratory differ slightly from those prepared elsewhere so must the interpretations of one laboratory differ from those of another It is impossible to dismiss the matter merely as difference in competence for both laboratories may take high rank on this score By a process of elimination, certain of these idiosyncratic variations can be seen, the result of experience to go back ultimately to the reputation and training of the serologist, his attitude toward the test, the technical make-up and changes in his staff, his clinical control and the irreducible false positive or relative positive-negative tendency of his laboratory

The serologic tests should not be performed as a side issue in small laboratories or by amateurs not under competent control The mastery of the mechanical technic is simple. The mastery of controls and possibilities of error the ability to find the source of trouble and the development of judgment in reading and interpretation of factors, is immensely difficult. Not every man who can gather the necessary bottles and test tubes is suited by training or temperament for the exercise of sound serological judgment. In the Copenhagen Conference of 1928, the absolute inevitability of false positives in the performance of the complement fixation type of test, even by masters of the art, was demonstrated beyond peradventure If as high as 14 per cent of false results could be obtained under such rigid conditions of control, it may be easily imagined that under less strictly regulated conditions there must be laboratories which are veritable mills of false positive reports, fastening suspicion of syphilitic infection right and left upon persons who do not have the disease. The newer types of procedure, in spite of their enormous increase in accuracy and dependability are not free from criticism on this score in spite of the infallibility with which the laboratory man is inclined, at times, to invest his favorite technic. Nor does the large laboratory giving a centralized service over a wide field of clinical pathology escape these difficulties. One of the most serious sources of error in larger laboratories is the changing about of technicians from one field of duty to another Dependable serological tests are produced year in and year out only by that form of adeptness which is developed by unbroken application to the work. Frequent false positives are the product of inexperience and overenthusiasm The amateur serologist himself approaches this problem too often with the attitude of a prosecuting attorney and boasts of his ability to prove a positive. False positives thus obtained are diagnostic malfeasances of the gravest type There are few laboratory procedures whose inevitable margin of error entails more social and personal suffering than the Wassermann reaction. Whatever savors of technical inexperience of the injudicious and uncritical temperament, of personal motive and purely commercial interest, of haste inaccuracy unpreparedness and pigheadedness, has no place in its performance The best results do not necessarily come from large establishments but rather from those in which personally skilful performance and supervision are available

In general, the serologist himself or a technician of years of experience only should read the results Inexperience at this particular point sends out broadcast flurries of false weak positives which may do inestimable harm, not only to the persons concerned as patients but to the confidence of the profession in the reaction In the same way a serologist temperamentally ultraconservative, by refusing to consider or report as *indeterminate* the partial positives he observes may materially reduce the efficiency of the test

Sensitivity vs. Specificity.—The physician who uses the serological tests for syphilis must clearly understand the rival claims involved in the title of this paragraph. Every advance in the sensitiveness of a serological test for syphilis—that is, in its ability to identify the disease in the absence of clinical signs—must be measured against the risk of pinning a partial or completely false positive finding upon a person who does not have the disease. It is proper therefore at the outset, to distrust the enthusiasm which recommends a new type of procedure or a pet hobby in the serological field as "highly sensitive." It is more important, for practical purposes, in our opinion that high *specificity* rather than sensitivity be accepted as the primary recommendation of a serological test procedure The more recent methods take careful account of both factors, as, for example, in the presumptive and diagnostic types of procedure recommended by Kahn and Kline for their respective precipitation tests. Kahn (1942, Serology) has pointed out that in 40 000 hospital admissions with 1200 cases of treated and untreated syphilis among them, an increase of 1 per cent in sensitivity means 12 cases of treated or untreated syphilis reported positive while 1 per cent increase in nonspecificity (loss in specificity) means 400 nonsyphilitic persons reported positive. By the older methods, specificity was weighed against sensitivity in the complement fixation reaction by the multiple antigens employed and highly cholesterinised antigens were ultimately very properly distrusted A part of this oversensitiveness can be controlled by using a highly sensitive test procedure for the initial examination so-called "screen test" of the serum, only the positives thereafter being subjected to the control of several methods of a less degree of sensitiveness. It has been considered proper to apply highly sensitive methods of testing to the serum of known syphilitic patients under treatment, in order to detect the slightest degree of positiveness as a guide to continuance

The efforts of Eagle to increase enormously the sensitiveness of serological tests will probably find their best application in this field rather than in that of diagnosis, although it has been the hope of certain investigators (Hinton) as yet unestablished that such combination of sensitivity and specificity might ultimately be obtained as to permit of the complete disappearance from clinical practice of that perplexing and disturbing combination, the negative blood and the abnormal or positive spinal fluid Kahn points out that limitless sensitivity is an inherent capacity of serologic tests, controllable by technical means including temperature conditions, etc. and that by appropriate steps, nearly all persons can be shown to give positive reactions for syphilis. In reading the literature, therefore, the practicing physician, particularly if he has power to influence a technician or laboratory should interpret with great conservatism all claims to high sensitivity unless they are accompanied by unescapable evidence of an equally high degree of specificity

Immune Body and Syphilitic Reagin Relations.—The original conception of the Wassermann reaction was that of a specific antigen-antibody reaction Many attempts have been made to reconcile the nonspecific reactivity of tissue lipoids employed as antigens and the conception of spirochetal products as the actual specific antigenic substances in serologic tests for syphilis Opinion, influenced by the work of Sachs, Klopstock and Weil (1925) leaned for a time towards nonspecificity of the antigen. Recent studies of Beck (1939) Kolmer and his associates (1941, 1942) and Eagle and his associates (1940) have tended to indicate that serologic tests for syphilis do partake of the nature of an immune body antigenic reaction, but the degree of specificity involved still remains a matter of dispute. The work initiated and stimulated by Gaehtgens (1929) who employed a special spirochetal antigen ("palligen")

a phenolized salt suspension of the so-called Reiter strain of alleged *Spirochaeta pallida* has been carried forward separately by Kolmer and by Eagle with strong indications that this particular spirochetal strain (and also the Kazan strain) has high specificity Eagle and Hogan are inclined to accept this rather high degree of specificity as distinctly due to a syphilis spirochetal antigen-antibody reaction. Kolmer and his coworkers seem more disposed to regard the reaction as in part due to natural group spirochetal antibody contained in human and in some animal blood which as well as that produced in syphilis, reacts not only with cultivated *Spirochaeta pallida* but with *Spirochaeta macrodentium Spirochaeta microdentium* and other spirochetes This spirochetal complement fixing antibody is increased in syphilis, malaria and leprosy and under the conditions, Kolmer believes, it is improbable that the spirochetal complement-fixation test will identify as biologic false reactions the positive Wassermann and flocculation reactions observed in nonsyphilitic persons with leprosy and malaria.

Specificity of Tests in the Light of Spirochetal Antigen Studies.—Kolmer and his coworkers believe that syphilitic antibody is distinct from the syphilitic reagin. Eagle and Hogan have thus far insisted that the two are probably identical. One point at which this difference of opinion would seem to be subject to test concerns the incidence of false positive reactions in diseases in which an abnormally high proportion of these reactions for syphilis is known to occur Thus lower specificity of the spirochetal antigen complement fixation reaction on the blood resulted in the Washington Serology Conference (1941) as compared with a number of the standard flocculation and complement fixation tests used in the serodiagnosis of syphilis. But in the cerebrospinal fluid where there is little or no natural spirochetal complement fixing antibody (Kolmer) the spirochetal antigen tests gave a high degree of specificity It would seem to the clinical mind that a type of reaction giving lower specificity with a supposedly more highly specific mechanism would be almost a contradiction in terms. The Kolmer conception, allowing for variation introduced by group spirochetal antigens and the separate identity of reagin and syphilitic immune body would be the more logical alternative.

Syphilitic Reagin in Normal and Apparently Nonsyphilitic Human Blood and in Animal Blood.—Increasingly critical examination of the mechanism of serologic tests for syphilis has shown as already indicated that on the one hand serologic tests can be made so sensitive that all persons will yield positive results on the blood serum and on the other that the serum of many persons apparently normal and of persons the victims of other infections and conditions may show measurable and even highly significant amounts of syphilitic reagin responsible for biologic false positive reactions. That the serum of a number of animals gives in varying percentages, positive results to serologic tests for syphilis even though the animals are known to be incapable of inoculation with the disease, should not, as Kemp Fitzgerald and Shepherd (1940) have indicated be regarded as an evidence of unreliability of serologic tests for syphilis in man. Many observers, including Kolmer Eagle, Kemp and Chesney have shown that complement fixation technics can be so modified for example, that they are always negative in nonsyphilitic rabbits and regularly positive at the height of the infection in syphilitic rabbits, notwithstanding the fact that a certain proportion of rabbit sera react positively to complement fixation tests for syphilitic reagin under certain modifications of technic. The whole subject of positive serologic reactions

for syphilis in animals is well reviewed by the above-named authors Kemp Fitzgerald and Shepherd.

In 1931 Malloy and Kahn succeeded in showing that when normal serum is mixed with standard Kahn antigen microscopic aggregates gradually form They were able to establish quantitative relations between the areas of aggregation developed during various periods of exposure for normal sera, and for syphilitic sera mixed with a standard and a sensitized Kahn antigen as used in the Kahn presumptive test. As the authors put it, "It appears that the difference between nonsyphilitic and syphilitic serum is one of degree rather than of kind that it is quantitative rather than qualitative. What occurs in syphilis is the increase of a lipoid aggregating quality possessed nonetheless even by nonsyphilitic sera. Pierce and Breazeale (1942) summarize experiments with plant saps and adsorbents such as calcium and sodium zeolite in which they find evidence that "reagin" is a divalent sodium or magnesium cation participating in a base exchange reaction. The beef heart antigen acts as a zeolite in producing a floc. The work is as yet unconfirmed. Schreus and Foerster (1934) Barnett, Jones and Kulchar (1935) devised methods and accomplished the demonstration of syphilitic reagin present even in the sera of nonsyphilitic individuals. These observations have been confirmed and Eagle, in an elaborately conducted and controlled survey of 40,545 students sera, estimated the incidence of one false positive reactor in every 1125 students as the probable normal for the biologic false positive Statistically corrected for other considerations, this proportion fell to one in every 4000 persons tested Mohr Moore and Eagle (1941) in the second and third papers of a series, have concentrated increasing attention by case studies and otherwise on the problem of biologic false positives, indicating particularly its close association with febrile infections, both of known and unknown character More detailed consideration of this problem is given below

Methods for Identifying Minute Amounts of Syphilitic Reagin.—Lund (1942) has developed as an offshoot of a medicolegal technic for the demonstration of agglutinins in dried blood stains, a centrifugalization procedure for the concentration of minute amounts of syphilitic reagin in blood serum This method has as yet only investigative significance but may constitute an important approach to the study of the biologic false positive reactions in normal and abnormal persons

Daily Variation of Reagin Content of Syphilitic Serum—This has long been regarded as a basis for fluctuating and alternating positive and negative reactions in serial tests on syphilitic and nonsyphilitic individuals. If the work of Mohr and Smith (1940) is confirmed, a large part of this clinically recognized daily variation will have to be assigned to the category of technical rather than biological error or variability Mohr and Smith showed by collecting and freezing a series of sera that the variability in reaction as between individual successive specimens practically disappears when a series of frozen specimens is examined at one and the same time Daily variability in serologic results is the basis of the clinical repetition of serologic tests in the investigation of possible false positives and positive-negative conflicts (Wassermann positive series) It is probably also a leading factor in the provocative procedure to be presently mentioned.

Reagin Titration in Diagnosis and Treatment.—As an aspect of the increasing emphasis on quantitative procedure in serodiagnosis in the attempt

to arrive at greater accuracy note should be made of the increasing use of the arbitrary "reagin titer" system of estimating the actual concentration of syphilitic reagin in a serum as measured by the particular serologic method used Moore and Eagle (1941) wisely point out that reagin titer varies with the technic, and even in the unavoidable variations in day-to-day sensitivity investigated by Mohr and Smith It is accordingly essential in interpreting reagin "units" as reported by various laboratories including for example those of the New York State Department of Health to realize that they are significant only as basis for comparisons or estimations when compared with other results obtained by an identically similar testing technic. The question as to whether reagin titer should be reported with the result of a test is one for much discussion but we believe on the whole such reports are more confusing than helpful in routine diagnostic work. In watching the increasing concentration of reagin developed in the serum of the syphilitic child seronegative or only weakly positive at first, quantitation of this type however becomes of considerable clinical importance. This will be considered more fully under the diagnosis of congenital syphilis (see also Fig 49)

Moore and Eagle (1941) established the fact that titer determined by their technic in complement fixation tests varied from 0 to 1000 units of reagin In primary syphilis the mean titer was 104 5 plus or minus 15 74 units in secondary syphilis the mean titer was 179 0 plus or minus 7.54 units. In various aspects of late syphilis, mean titer varied from 21.5 to 41 1 units. Latent syphilis and tabes dorsalis gave significantly lower titers than other aspects of late syphilis. The reagin titer of the blood can be reduced by treatment with or without clinical improvement, is not an expression of the severity or gravity of the syphilitic infection in the individual patient. The authors believe the reagin titer to be definitely related to the numbers of organisms present in the tissues of the host. The authors conclude that a single quantitative test before treatment is of no diagnostic or prognostic importance Further investigations by Crosby and Campbell (1941) indicated that there is an apparent provocative effect in the second week of treatment of seronegative primary syphilis as gauged by reagin titer but that this does not develop in seropositive primary or early secondary syphilis, is probably more apparent than real. Race, sex and age do not demonstrably affect initial reagin titer or its response to treatment nor is it influenced by the presence or absence of spinal fluid abnormalities The coexistence of pregnancy in early syphilis is also without effect the same can be said of the season of the year (winter vs summer) In the study of the course of so-called "serologically fast" syphilis, reagin titration, while the ordinary test reveals consistently strong positives, may indicate declines ranging from as high as 200 to 800 to as low as 4 units by the twentieth serial examination.

Quantitative Serologic Testing of Blood and Spinal Fluid.—Answering the demands created by Kolmer's quantitative Wassermann, the majority of complement fixation and precipitation procedures used in the diagnosis of syphilis now have quantitative modifications dependent on the use of serial dilutions of serum for expressing the approximate strength of the reaction. Kahn (1939) gives a good summary of the various reasons why a quantitative test has value, which can be briefly summarized as follows In questionable cases it is assumed that high titers are of greater diagnostic significance than low titers. Quantitative tests are assumed to gauge to some extent the activity of the syphilitic infection Quantitation may assist ultimately in differentiat

as much nonspecificity and quantitative versus qualitative variability as the serologic test for syphilis. Such confusion can be resolved only by conference and cross-check, by agreement among authorities as to the most acceptable standard procedure, and by their repeated and determined evaluation and reevaluation under the supervision not only of the laboratory but of the syphilis clinic.

It is now an established fact that even when performed by the originators under seemingly [illegible] but at different times and in different places, the most dependable [illegible] serologic tests do not give uniform results either [illegible]. That this statement applies both to precipitation [illegible] tests; that complement fixation tests will [illegible] tests are negative, and the reverse; that multiple [illegible] type may give, when used "in battery," a confusing [illegible] from flat negatives to strongly positive [illegible] the fact that no single serologic test and no combination [illegible] in our present knowledge give the inquiring physician [illegible] verdict as to whether or not the blood specimen [illegible] reagin in sufficient amount to demonstrate [illegible]. After all, one familiar with the history [illegible] the diagnosis of syphilis, finds less matter for [illegible] incertitude than he would find in the demonstration [illegible] exact and unvaryingly uniform test. The present use [illegible] mingling complement fixation and precipitation [illegible] in the history of serologic diagnosis the use [illegible] variations in temperature, dilutions, complement, salt [illegible] ingredients which characterized the over-refined test procedure [illegible] ago. Today the laboratory either on its own initiative [illegible] pressure of syphilologic or general practitioner demands attempt [illegible] at least too much rather than too little. The result, as Moore and Eagle point out, is simply confusion thrice confounded. That serologists, syphilologists and practitioners all find themselves in such a dither over serologic test discord and nonconformities is essentially a tribute to our tendency to serologism, the disposition to diagnose syphilis by blood-tests. On the one hand, Schoch will insist on two different tests and endeavor to reconcile their variable results in conjunction with the general examination for syphilis, while Moore and Eagle will insist that even though the results of multiple tests be reported to the physician submitting the specimen, it is the business of the serologist to head his report by a final evaluation which represents the serologist's opinion as to the presumption established by the multiple tests' results. Between these two extremes all sorts of procedure exist. Substantial agreement has been reached as the result of international and national conferences on the following points:

1. Absolute uniformity among test results on a single specimen cannot be expected.

2. Precipitation tests should be supplemented by complement fixation procedure either performed routinely or available if the result of the precipitation test is doubtful.

3. In the opinion of [illegible] only five procedures are sufficiently well performed by a sufficient number of laboratories to deserve the title of "approved." These are the Kolmer Wassermann test, the Kahn, Eagle, Hinton and Kline precipitation procedures. While there is no bar advisable to the performance of other types of test, they should be regarded in the effort to provide dependable national serologic service as research procedures rather than practice procedures. If additional tests are performed by any laboratory they should be a matter for supplementary

to arrive at greater accuracy note should be made of the increasing use of the arbitrary "reagin titer" system of estimating the actual concentration of syphilitic reagin in a serum as measured by the particular serologic method used. Moore and Eagle (1941) wisely point out that reagin "titer varies with the technic, and even in the unavoidable variations in day-to-day sensitivity investigated by Mohr and Smith It is accordingly essential in interpreting reagin "units" as reported by various laboratories including for example those of the New York State Department of Health to realize that they are significant only as basis for comparisons or estimations when compared with other results obtained by an identically similar testing technic The question as to whether reagin titer should be reported with the result of a test is one for much discussion, but we believe on the whole such reports are more confusing than helpful in routine diagnostic work. In watching the increasing concentration of reagin developed in the serum of the syphilitic child seronegative or only weakly positive at first, quantitation of this type however becomes of considerable clinical importance This will be considered more fully under the diagnosis of congenital syphilis (see also Fig 43)

Moore and Eagle (1941) established the fact that titer determined by their technic in complement fixation tests varied from 0 to 1000 units of reagin In primary syphilis the mean titer was 104.3 plus or minus 13 74 units in secondary syphilis the mean titer was 170 6 plus or minus 7.54 units. In various aspects of late syphilis mean titer varied from 21.5 to 41 1 units. Latent syphilis and tabes dorsalis gave significantly lower titers than other aspects of late syphilis. The reagin titer of the blood can be reduced by treatment with or without clinical improvement, is not an expression of the severity or gravity of the syphilitic infection in the individual patient. The authors believe the reagin titer to be definitely related to the numbers of organisms present in the tissues of the host. The authors conclude that a single quantitative test before treatment is of no diagnostic or prognostic importance. Further investigations by Crosby and Campbell (1941) indicated that there is an apparent provocative effect in the second week of treatment of seronegative primary syphilis as gauged by reagin titer but that this does not develop in seropositive primary or early secondary syphilis, is probably more apparent than real. Race, sex and age do not demonstrably affect initial reagin titer or its response to treatment nor is it influenced by the presence or absence of spinal fluid abnormalities The coexistence of pregnancy in early syphilis is also without effect the same can be said of the season of the year (winter vs summer) In the study of the course of so-called "serologically fast syphilis, reagin titration while the ordinary test reveals consistently strong positives, may indicate declines ranging from as high as 200 to 800 to as low as 4 units by the twentieth serial examination.

Quantitative Serologic Testing of Blood and Spinal Fluid.—Answering the demands created by Kolmer's quantitative Wassermann the majority of complement fixation and precipitation procedures used in the diagnosis of syphilis now have quantitative modifications dependent on the use of serial dilutions of serum for expressing the approximate strength of the reaction Kahn (1939) gives a good summary of the various reasons why a quantitative test has value, which can be briefly summarized as follows In questionable cases it is assumed that high titers are of greater diagnostic significance than low titers Quantitative tests are assumed to gauge to some extent the activity of the syphilitic infection. Quantitation may assist ultimately in differentiat

ing the biologic false positives of leprosy malaria and infectious mononucleosis as well as other nonsyphilitic diseases from syphilis. Quantitative reactions may be helpful in estimating the effect of treatment, especially in latency and for measuring the relative effectiveness of differing methods of treatment. Quantitation may indicate the oncoming of relapse and of favorable response in serologically resistant or "fast" cases Kahn recognizes a provocative rise and subsequent drop in quantitative values when treatment is initiated. Such a rise may be used in the interpretation of a therapeutic test. Quantitative testing is of great importance in the diagnosis and therapy of neurosyphilis, as will appear in subsequent chapters since it is a part of the basis of prognostic grading employed in clinical work. Finally quantitation is of great value in recognizing the status of the new-born child of a syphilitic mother during the first few weeks of life

Of these various considerations we are disposed to place by far the greatest emphasis on quantitation in spinal fluid examinations and in the testing of the blood of the syphilitic or potentially syphilitic infant. In other aspects of syphilis particularly in gauging the effect of treatment in latency and in all other prognostic interpretation, quantitative serologic testing is as often unsatisfactory and untrustworthy as it is illuminating The systematic reporting of quantitative tests to the practicing physician is so generally a source of confusion and misinterpretation that except when specially requested, it should not be done. The attempt to use quantitation in serologic tests in serial tests, in interpreting the differences in results between differing laboratories and in attempting a provocative procedure is in the light of the most recent work a source of confusion and possible error rather than help The statement of Moore and Eagle that quantitative testing, to have significance must be performed consistently by the same laboratory in any one series of reports on a given case, must be borne in mind for quantitative testing as between different laboratories is a fertile source of misunderstanding and error As yet, no valid investigative basis exists for the use of quantitation in differentiation of biologic false positives from true syphilitic positives in doubtful cases The recommendation originally sponsored by the League of Nations Copenhagen conference in 1928 with reference to the form of reporting serologic tests in at most two or three grades of positiveness, has been even more closely drawn in recent practice. The original recommendation calls for reports of negative, plus-minus, one-plus and two-plus the last mentioned being *strongly positive* More recently the tendency has been to report for ordinary purposes in routine tests, either a definitive negative or a definitive positive If the positive is not definite it is not reported as plus-minus, weak positive one-plus or any similar designation, but by the use of the words "indeterminate-repeat. This reminds the physician that partial positives are difficult of interpretation or even uninterpretable and that safety first" calls for the repetition of the test procedure on a blood which gives less than a definitive positive reaction for syphilis. It may be said we believe, that serologists in general entertain the more positive convictions as to the validity of positive tests It is clinicians whose puzzling and difficult experiences with "fractionated" reports lead them to clamor for clear-cut positive or negative answers to their serologic questions and hesitate at weak positive " doubtful," and similar reactions Kolmer who developed what we believe to be the all-around most satisfactory quantitative complement fixation test for general use, himself insists that the designations "strongly positive and weakly positive

be retained For the expert, quantitation is an aid For the average practitioner it is more frequently a source of confusion or error

Zone Reactions as Sources of Confusion.—Eagle (1037) has excellently summarized the various types of zone reaction encountered in the serologic testing of certain serums, especially with the complement fixation procedure and occasionally in flocculation procedures (Wiener 1037 Greene and Breazeale 1030) in which lower dilutions of serum may give negative reactions while the high dilutions give positive results. A number of possible factors are involved and the problem is mainly one for technical interpretation by expert serologists

A negative reaction obtained with a screen, exclusion" or "presumptive" test on an actually positive specimen (Kline for example) is reported by Myers and Perry (1942) as a "prezone reaction observed in positive sera. It occurs to the extent of 0 0 per cent of routinely examined specimens.

Passing of the Provocative Procedure.—It is still conceded by a number of observers that a rise in the titer of syphilitic reagin occurs in syphilitics and in apparently normal persons, following the induction of antisyphilitic treatment, particularly with an arsenical. The increasing evidence of the presence of syphilitic reagin in the blood of normal persons its increase under nonspecific influences such as intercurrent infections its increase following the very procedures employed to cause its increase in syphilitic individuals and the demonstration that serial tests on any blood are subject to marked variation, especially in borderline degrees of positive serologic reactions for syphilis have all weakened confidence in the test to the point where it can no longer be recommended for general use as a diagnostic procedure. On the other hand, that a rise in reagin titer does occur as a species of Herxheimer like flare reaction in syphilis occasionally justifies the expert, thoroughly familiar with the interpretative pitfalls involved in using what might be called a provocative procedure as an aid in diagnosis A series of tests performed on successive days by quantitative technic may yield enough presumption of the presence of syphilis to help out in connection with other evidence A rise in the titer of reagin or increase in the strength of a positive on successive weeks, conjointly with the administration of weekly injections of a bismuth salt, is occasionally of assistance in a doubtful case The least trustworthy of the provocative procedures in our estimation at the present time is the one formerly recommended as standard namely the taking of successive blood specimens daily for a week, following a single injection of an arsphenamine. The factors of error here rise to such a degree of importance that the single injection arsphenamine provocative can no longer we believe, be recommended In addition, moreover the possibility of causing a harmful exacerbation of the infection (therapeutic shock) by the use of an arsphenamine in a diagnostic procedure of doubtful value still further weakens its justification Moore (1941 text) cites the work of Eagle, Mohr Hogan and Kemp in support of this last-mentioned viewpoint.

The Problem of Contradictory and Conflicting Serologic Results.—The progressive obscuring of the simple positive or negative statement desired by the average physician as the result of a serologic test for syphilis is an inevitability dependent on the steadily increasing number of modifications and improvements in serologic testing technics the conviction of authorities that their individual procedures have special merits and as can be seen from the foregoing discussion the confusion element inherent in a test that involves

as much nonspecificity and quantitative versus qualitative variability as the serologic test for syphilis. Such confusion can be resolved only by conference and cross-checks by agreement among authorities as to the most acceptable standard procedures and by their repeated and determined evaluation and reevaluation under the supervision not only of the laboratory but of the syphilis clinic.

It is now an established fact that even when performed by the originators under seemingly ideal conditions but at different times and in different places, the most dependable and widely accepted serologic tests do not give uniform results either as to specificity or sensitivity. That this statement applies both to precipitation and to complement fixation tests, that complement fixation tests will give positives when precipitation tests are negative and the reverse, that multiple methods and tests of either type may give, when used "in battery," a confusing burst of results ranging from flat negatives to strongly positive, is simply a demonstration of the fact that no single serologic test and no combination of serologic tests can in our present knowledge give the inquiring physician an absolutely definitive verdict as to whether or not the blood specimens tested contain syphilitic reagin in sufficient amount to demonstrate the presence of the disease. After all, one familiar with the history of serology and its relation to the diagnosis of syphilis, finds less matter for surprise in this inevitable incertitude than he would find in the demonstration of a single absolutely exact and unvaryingly uniform test. The present use of multiple-test procedures, mingling complement fixation and precipitation methods, simply replaces in the history of serologic diagnosis the use of multiple antigens, variations in temperature, dilutions, complement, salt solution and other ingredients which characterized the over-refined test procedures of a decade or more ago. Today the laboratory, either on its own initiative or under the pressure of syphilologic or general practitioner demands, attempts to provide at least too much rather than too little. The result, as Moore and Eagle point out, is simply confusion thrice confounded. That serologists, syphilologists and practitioners all find themselves in such a dither over serologic test discord and nonconformities is essentially a tribute to our tendency to "serologism," the disposition to diagnose syphilis by blood tests. On the one hand, Schoch will insist on two different tests and endeavor to reconcile their variable results in conjunction with the general examination for syphilis, while Moore and Eagle will insist that even though the result of multiple tests be reported to the physician submitting the specimen, it is the business of the serologist to head his report by a final evaluation which represents the serologist's opinion as to the presumption established by the multiple tests' results. Between these two extremes all sorts of procedure exist. Substantial agreement has been reached as the result of international and national conferences on the following points:

1. Absolute uniformity among test results on a single specimen cannot be expected.

2. *Precipitation tests should be supplemented by complement fixation procedure either* performed routinely or available if the result of the precipitation test is doubtful.

3. In this country at least, only five procedures are sufficiently well performed by a sufficient number of laboratories to deserve the title of "approved." These are the Kolmer Wassermann test, the Eagle, Kahn, Hinton and Kline precipitation procedures. While there is no bar advisable to the performance of other types of tests, they should be regarded in the effort to provide dependable national serologic service as research procedures rather than practice procedures. If additional tests are performed by any laboratory they should be a matter for supplementary

report and should not be admitted to the status of "approved" until their repeated evaluation in national serologic conferences establishes their distinctive superiority.

4. The specificity of serologic tests is in general more important than their sensitivity. *Specificity should be practically 100 per cent, and in laboratory grouping and approval status,* specificity rating below 99 per cent on 200 test specimens or 98 per cent on 100 specimens should lead to the temporary exclusion of the test from the approved list until such time as modification reestablishes a rating for it of 100 per cent. Sensitivity on the other hand—"an approved sensitivity rating shall be not more than 20 per cent below that of the control laboratory in cases of late or treated syphilis, and within 1 per cent of that of the control laboratory in cases of untreated and secondary syphilis."

For those interested in studying the range of variability of serologic tests on individual specimens or in mass testing, reference should be had to the studies of Shepler, Lyons and MacNeal (1928) (Arch. Dermat. & Syph. 18:748), who coined the term "serologic discord"; Pierce and coworkers (1938) (Am. J. Syph., Gonor. & Ven. Dis. 22:39); Crawford and Day (1939) (J.A.M.A. 113:1718); Moore and Eagle (1941) (J.A.M.A., 117:849); Hinrichsen (1941) (Supp. No. 14, Ven. Dis. Inform.); Hodel (1944) (Ven. Dis. Inform. 25:315); Kahn (1942) (Serology in Syphilis Control, Chapter X); Hinrichsen's admirable summary includes the condensation of the results of the successive American serologic test procedure evaluations as well as the League of Nations conferences.

Ultrasensitive Serologic Tests (Presumptive, Exclusion, Elimination and Screen Tests).—In the effort both to increase the certainty of detection of syphilitic reagin in significant amounts for the diagnosis of syphilis, to *exclude syphilis* from a diagnosis by serologic test, and to provide a shortened and less costly procedure as a preliminary to more elaborate serologic tests on selected specimens, a group of procedures, chiefly precipitation in character, has been built up. There is an undoubted utility in these supersensitive foreshortened procedures but simultaneously some very serious drawbacks. First, it should be insisted that there is literally no such thing as a test which will *exclude* syphilis from a diagnosis. The presumption based on the belief that minute amounts of syphilitic reagin are less significant than larger amounts may be established against syphilis, but an absolute exclusion is impossible on any serologic grounds alone. For this reason it has been several times emphasized that the term "screen" is preferable to "exclusion," and that the term "presumptive" admits into diagnostic appraisal a false emphasis on serologic test results which is constantly misused by the practicing physician in his strong predisposition to make a diagnosis of syphilis on serologic grounds whenever he is given the least opportunity to do so. The foreshortened and ultrasensitive tests have achieved a part of their popularity because like the substitution of precipitation procedure for complement fixation they make a "high positive showing on tested blood" possible as a demonstration of efficiency at minimal expense. (The point of view frankly so expressed in several letters from health and laboratory authorities.) Eagle in particular has expressed a belief with which we are in the main in accord that it is doubtful whether ultrasensitive procedure really shows anything trustworthy that the adequately performed original precipitation test could not have supplied. The disposition to boost the showing of positives in the work of the serologic laboratory by the selection of sensitive first-line tests is a regrettable form of bias in a procedure which, at best, can never wholly escape interpretative personal equations. If screen tests are to be employed the reexamination of doubtfuls and questioned positives or negatives should include a complement fixation procedure, preferably the Kolmer. Partial positives (except in treated cases) are not diagnostic, but rather interpretative and investigative material for specialists, and whether reported in titer

or in pluses, with or without the results of repetitions, should be distinctly understood to be of only limited significance. They should be referred to an experienced or even a syphilologic evaluator for interpretation if possible, and are dangerous sources of error when reported for diagnosis to the average doctor

It should then be a fundamental principle emphasized by Moore among others, that the results of presumptive tests should only be reported when negative, and never to the practicing physician when positive or partially positive The positives obtained in the laboratory should be immediately checked against standard procedures, and only the standard results reported. Moore further advises that the use of presumptive and exclusion tests be limited to (1) the serologic testing of donors for blood transfusion as an added safeguard for the prevention of transfusion syphilis (2) in syphilis clinics in which there is expert clinical interpretation, and (3) in following the results of treatment in patients definitely proved to have syphilis. Otherwise used, the presumptive test result reported as a routine invites a margin of error ranging from 2 per cent to nearly 9 per cent of false or nonspecific results in nonsyphilitic patients Because of zone reactions, even the screen tests have so significant a margin of error that it is questionable whether they should be used at all as trustworthy screen procedures except in case of emergency or special circumstances.

The Expanding Field of Biologic False Positive Reactions.—The clinical syphilologist of twenty years ago found himself obliged continually to impress upon the practicing physician the ubiquity and importance of the false negative serologic test in the presence of syphilis. The syphilologist of today has almost completely reversed the position. He finds himself confused by the uncertainties of the positive and loud in warning not to accept the single the partial or even the repeated positive blood test as final evidence of the presence of syphilis In a way the present position threatens the intelligent use of serologic tests for syphilis far more than did the doubt attaching to the negative. Inevitably faith in the positive is being undermined and with it, the tremendous positive efficiency and low margin of error of serologic test procedure for syphilis in the aggregate is momentarily submerged

Intralaboratory (Multiple Test) Interlaboratory and Laboratory-Clinic Control.—The modern serological laboratory has, sometimes reluctantly it must be confessed finally begun to yield to the pressure of growing knowledge and to accept intra and extra-laboratory and laboratory-clinic controls in its syphilis serodiagnostic work. But the path of the syphilologist determined to invade the sanctum of the laboratory potentate with his demand for checks, has been by no means an easy one. Few laboratories as yet feel themselves obliged to check a series of bloods periodically against the findings of another laboratory A larger proportion of laboratories now perform two test procedures, one complement fixation and one precipitation, as checks against each other The large majority of the smaller or independent laboratories and even some of the larger institutions in this country at least, perform only a Wassermann test or the particular precipitation test which has been devised by the serologist at the head of the laboratory A few laboratories lean over backward in the opposite direction by performing multiple procedures in the effort to insure to their clinicians a report which shall leave no stone unturned no furrow unopened in the serological diagnosis of their cases. The inevitable result, in this last group is expensive and unnecessary reduplication with

confused and conflicting reports that make the serological going for the average physician as difficult as that on foot over a plowed and rocky field. Very few laboratories indeed have available or show themselves disposed to submit to syphilis-clinic control. It will be an evidence of the advance of a broadly modern syphilology when our serological brothers accept the copartnership and final voice of the syphilis clinic in the ultimate interpretation of serological results.

The Control of Laboratory Results.—The items which require periodic investigation in the serological work of a laboratory are the *false negative tendency* of the laboratory, the *false positive tendency*, and the maximum positive efficiency.

The false negative tendency, or tendency to yield negatives instead of positives in syphilis, is checked either for a test or a group of test methods by the running of known syphilitic sera. Two technics within the same laboratory may be compared with each other in this way; but a more satisfactory comparison is that between two laboratories using identical sera with either the same or different procedures. On several occasions when we have been called on to cooperate in such checks, we have been astonished at the proportion of negative results obtained in undoubted syphilis by serologists who were entirely unaware of the trend of their methods. The increased sensitiveness of present-day procedure is however greatly reducing the false negative tendency. Such declines in efficiency are sometimes due to changes in technical staff without change of method, and may amount to as much as a decrease of 50 per cent in the number of positive reactions rendered over a period of six months.

A second method of testing for *false negative tendency* can be found in the repetition of tests on the same patient. If a patient's serum yields a strong positive on one day and a complete negative on a *fresh specimen* the next day, this may be within the bounds of fortuitous variation, though improbably so. But when on repetition in undoubted untreated syphilis, positives with the first test are returned as positives with the second test only once in seven times, the remaining six being reversals to negative, the procedure is probably insensitive.

A third method of checking *false negative tendency* and the sensitiveness of a laboratory's results, is by comparing the ratio of partial positives to strong positives over a period of time. A marked increase in the proportion of weak positives reported may, of course, mean an overdelicate test, but when the average incidence of strong positives from the laboratory over a period of several years is known, a decline in the number of strong positives and an increase in the proportion of weak positives means an insensitive technic. In one such examination of a laboratory's results, the proportion of weak to clear-cut positives changed in six months from a ratio of 1 : 5 to a ratio of 1 : 1.8, while the total incidence of all positives obtained fell from 8 per cent to 3.4 per cent of all tests made. These declines in efficiency may take place most insidiously, and without constant vigilance and the best cooperation of clinician and serologist, may create a most mistaken impression of the prevalence of syphilis in the clientele and be responsible for many errors of omission in diagnosis.

The False Positive Tendency.—The *false positive tendency* of a laboratory can be determined in part by a duplicate performance of tests on identical sera by different laboratories over a period of several weeks or months. This interlaboratory check, however, is uninterpretable unless a third party to the arrangement exists in the form of a competent syphilis clinic which provides the medical decision as to the weight of evidence for or against syphilis in the given case. Individual false positives can be picked up and in part verified as such, by repetition of the test, and this method the clinic perforce must apply in a good many cases where the evidence for or against, from the clinical side, is scanty or debatable.

One of the best controls of false positive tendency is the daily report sheet of the laboratory performing tests for a large number of clinicians and patients. The admirable cooperation of Sanford during Stokes's Mayo Clinic experience made possible in this way the detection of most of the inevitable false positives that occur in the work of every laboratory. On the report sheet

false positives show tendency to occur in clumps, and the identification of three or four as occurring in single small rack of tubes t once rouses suspicion, both in the laboratory and in the clinic.

It is a mistake to suppose that the controls established for the Wassermann test in the laboratory itself are adequate to prevent the occurrence of false positives and the writers believe that the same statement applies even to precipitation tests simultaneously performed for control purposes That is, both Wassermann and Kahn for example on a single serum may be reported positive or negative and yet the report be false The differentiation of biological from technical false positives, also essential to the interpretation of the results of a laboratory is discussed under the positive Wassermann test.

Maximum Positive Efficiency.—Every laboratory should be periodically checked for its maximum positive efficiency against the blood of known untreated acute secondary syphilis and untreated early but clearly defined general paresis. The blood in both these phases of the disease is so nearly universally positive that a laboratory whose test procedures yield less than 99 per cent (and some observers insist even on 100 per cent) positives in these two phases of the disease should be regarded as running insensitive procedures.

Appraising a Laboratory.—The general work of a serological laboratory can be appraised to some extent through observation of its way of meeting the various possible factors of error previously described Technicians on rotating or frequently changing service glassware cleaned in casual fashion, numerous or repeated anticomplementary reports, flocks of unexplainable weak positives repeated and striking but unsystematized differences between multiple antigens, all very properly arouse the suspicion of the clinician who must interpret laboratory results to the patient himself Laboratories performing single Wassermann tests, laboratories which in this day decline to introduce precipitation procedures, laboratories which render partial, unsatisfactory reports on spinal fluid examinations when the fluid supplied was fresh, free from blood and sufficient in quantity all fall within the twilight *zone of possible unreliability*

What the Serologist Is Entitled to.—In exchange for his response in this matter the serologist has an equal right to check and inquire into the quirks, prejudices, foibles and false trends of his clinical associate He should receive for testing a specimen drawn and handled in accordance with the technic already described If inactivation is employed in the laboratory serological technic this should be performed as soon as possible after the blood is drawn and refrigeration should be maintained both before and after inactivation. The quantity of blood should be not less than 5 nor more than 10 cc., labels should be legible, affixed immediately and held in place not only by paste but by rubber bands. The proper requisition form should be made out in legible fashion and accompany the tube to the laboratory Much injustice has been done serologists, particularly by isolated practitioners, in criticizing reports based on thoroughly unsatisfactory material submitted for examination.

A LIST OF SEROLOGIC TESTS FOR SYPHILIS

A. **Approved Serologic Tests** (American practice) See Supplement No. 11 Venereal Disease Information, 1940, for complete technics.

1. *Complement fixation technics*
   a. Kolmer Wassermann.
   b. Eagle-Wassermann.

2. *Flocculation technic* (standard):
    a. Kahn standard.
    b. Kline diagnostic.
    c. Eagle macroflocculation.
    d. Hinton.
3. *Screen flocculation* (supersensitive for special purposes):
    a. Kahn presumptive.
    b. Kline exclusion.

B. Some New and Old Tests (not fully evaluated or not generally used in American practice).

1. *Complement fixation technic:*
    a. Medical Research Council No. 1 (British Ministry of Health)—cholesterinized human heart extract—4-tube set-up, sheep cell hemolytic system, with variable amounts of complement.
    b. Boerner and Lukens (B. L.)—simplified test; chief difference from Eagle and Kolmer complement fixation tests: mixing of certain of the reagents in bulk and use of optimum doses of complement, hemolysin and antigen in place of units.
    c. Spirochetal (Gaehtgens "Palligen")—antigen from Reiter and Kazan strains of *Spirochaeta pallida*, usable especially on cerebrospinal fluid; specificity on blood not exceptional.
    d. United States Army Wassermann—hemolytic system, antihuman.
    e. New York State Department of Health—Wadsworth, Maltaner and Maltaner (1936)—quantitative; used since 1937.
    f. Hecht active complement fixation method.
2. *Flocculation technic:*
    a. Boerner-Jones-Lukens—microscopic and macroscopic; beef heart antigen prepared by simple technic, using acetone in preliminary extraction followed by ether alcohol extraction.
    b. Davies micromodification of Hinton—micromodification of the Hinton test.
    c. Mazzini—slide flocculation test based on use of beef heart and egg yolk extract in antigen.
    d. Laughlen—employs special modification of Kahn antigen (Kahn antigen plus cholesterol, scarlet red dye and balsam); colored reaction.
    Eagle microflocculation—micromodification of Eagle flocculation test, using 0.1 cc. serum; antigen from beef heart fortified with cholesterol and corn germ sterol.
    f. Meinicke—active instead of inactivated serum, horse heart extract diluted with alcohol to which balsam of Tolu and benzoic acid are added.
    g. Müller Clotting ("Ballungs")—alcoholic cholesterinized ox heart allowed to mature in thermostat. Uses inactivated serum.
    h. Ide—coloring method, alcoholic (95 per cent) extract of beef heart muscle containing 0.2 per cent cholesterin to 100 cc. of which are added 5 cc. of 5 per cent solution of gum benzoin, and 0.1 cc. each of 1 per cent alcoholic solution of crystal violet and azure II.
    i. Chediak—micro-test, employing a drop of dried blood.
    j. Strauss slide modification of Kahn and Eagle.
    k. Sachs-Georgi—direct flocculation of cholesterinized extract (ox). Two procedures: "lentochol" (slower) and "citochol" (more sensitive, less specific).
    l. Murata test (Sachs and Witebsky)—ring modification of Sachs-Georgi test.
    m. Sigma reaction—cholesterinized alcoholic extract of calf's heart.
    n. Vernes—elaborate test; special reagents and apparatus; read for day to day variation, uses horse heart in antigen.
    o. Leiboff—colored reaction.
    p. Levy—antigen mastic flocculation.
    q. Marquez (Rein-Hazay modification).
    Sellek—Frade II.
    s. Dyts.

C. "Verification" Tests

1. *Kahn* (temperature test) for differentiation of true from false positive reactions by performance of Kahn test at 1° C, 37° C and 57° C. (Not satisfactory test.)
2. *Kahn* (new) *salt concentration test*, specific and nonspecific serologic reactions are affected differently by certain concentrations of sodium chloride. (Not evaluated.)

D) Choice of serologic test for serum:

A survey of results obtained with the tests under consideration by the Washington Serologic Conferences (1935–1940) in all five of the evaluation studies in which they were used gave definite indications of the relative value of the different American tests. Only in the first evaluation study were the syphilitic patients classified as primary secondary and late syphilis. The Kahn presumptive the Hinton, and the Kline exclusion tests were the most sensitive tests in primary syphilis, giving 82.9 81.0, and 80.5 per cent of positive reactions, respectively the Kahn standard, the Kline diagnostic, the Eagle flocculation, and the Kolmer gave 79 7 74 4, and 72.1 and 63.9 per cent of positive reactions, respectively in primary syphilis. All of these tests were 100 per cent positive in secondary syphilis. In late syphilis the Hinton, Kahn presumptive, Kline exclusion, Eagle flocculation, Kahn standard, Kolmer and Kline diagnostic tests gave the following percentages of positive reactions, respectively: 84.5 84.5, 83.0, 82.4 76.9, 72.1 and 71.5. However sensitive test is valuable only if it is specific at the same time; in fact, specificity is much more important than extreme sensitivity if choice between the two characteristics has to be made. In the first evaluation study the Hinton gave 0.7 per cent of false positive reactions, the Kahn presumptive 3.3 per cent, the Kline exclusion 0 7 per cent, the Eagle flocculation 2 0 per cent of false positive reactions, the other tests having 100 per cent specificity In other words, the three most sensitive tests were also the most unreliable tests in this first study The tests hich gave false doubtful reactions in two or more of the four evaluation studies were the Hinton, Kline exclusion, Kahn presumptive, and Kline diagnostic tests. The Eagle complement fixation reaction as done only in the second, fourth and fifth studies in which it was 100 per cent specific. The most outstanding test in regard t specificity is the Kolmer test. In all 5 evaluation studies it was 100 per cent specific and gave even among the syphilitic serums only one doubtful reaction. In the first two studies its sensitivity was rather low in comparison, being 72.1 (late syphilis) and 59 0 per cent respectively However in the last three studies its sensitivity compares very favorably with that obtained with other tests which were less specific.

The Kahn presumptive and Kline exclusion tests are not specific enough to be used as diagnostic tests.

The flocculation procedures are inferior to complement fixation in testing spinal fluid.

E. Some Additional Principles

1 Frequent departure of users of test from the details of the originator methods, is common source of error
2. Short-cuts and obsolete technics are source of error
3. The control serologists (originators of principal tests) had only 4 false positives in 4 years. As of 1940, one fourth of the State laboratories were doing superior work. Thirty were doing unsatisfactory work in 1936, 22 in 1939
4. Two tests should be performed for the final evaluation of all specimens—either two of the same type (complement fixation or flocculation) or one of each type. A single test leads to errors. Technicians should receive basic training at laboratory control centers or originators laboratories, for the tests they are to perform.
5 The recommendation that plus marks be dropped in the reporting of serologic tests for syphilis, and that the words, "positive, doubtful, and "negative be used instead, first made at the League of Nations serologic conference at Copenhagen in 1923, was accepted and recommended for American procedure. The definition of doubtful" however continues to be matter of uncertainty and number of serologists (Wadsworth, Cannelmas) and syphilologists feel that some form of definition (reagin titer report, etc.) should be offered the physician to aid in interpreting this category

THE CLINICAL ASPECTS OF THE INTERPRETATION OF SEROLOGICAL TESTS

The Positive Serological Test.—There is inevitably a certain amount of overlap in the discussion of clinical as contrasted with laboratory problems in the interpretation of serological tests. At the same time it is worth while to give the clinical side some degree of special emphasis. The habit of accepting without dispute the report of a laboratory is so firmly impressed upon the present generation of physicians that it is necessary to drive home with more than ordinary force the statement that no serological laboratory no matter how well and conscientiously conducted is ever always right in its reports

Fig 34.

A SUMMARY OF LIMITATIONS AND POSSIBILITIES IN SEROLOGICAL TEST CONTROL (LABORATORY PHASE)

1 The Physician's desire for consistent 100 per cent specificity nd sensitivity and bsolutely clear-cut report cannot be met by any serological test or combination of tests for syphili in routine performance today Agreement on positive results in tests performed by groups of serologists ranges from 78 t 100 per cent.

2. Agreement between tests however is not tantamount t clinical accuracy

3. Disagreements must be expected:

a. Between antigens in the same W ssermann test

b. Bet een the results of two or more tests in the same laboratory on single serum. This is true sometimes even hen the tests are of markedly different type (as in kolmer W ssermann and kahn precipitation tests), or when they are similar (Eagle Hinton and Kline)

d When the same serum is tested in two different laboratories even by supposedly identical methods.

When the serum of lat and latent syphilis or yphilis in pregnancy is tested by any group of different method (serological discord)

f When the serum of the same patient is repeatedly tested by identical methods on successive days or t longer interval

g When treatment has intervened to lter the routine expectancy indicated in Figs. 38 t 41

4 Th frequency of disagreement and the margin of inevitable error diminishes ith the perfection of technical performance but it has never completely disappeared.

5 Essential elements in securing maximum reliability in performance by the laboratory are

A good specimen; stable experienced technical service cle glass fresh animal (Wassermann test) uniform expert reading conditions, voidance of the experimental in routine reports, a nonpartisan serologist; strict adherence t the originator technic and his modifications of his method.

b. Approved" laboratories { Intralaboratory check by multiple tests (but not too multiple) Interlaboratory exchanges of sera periodically for test purposes.

c. Laboratory-clinic check, against the opinion and experiences of syphilis clinic (state and cit laboratories should note, as well commercial groups).

6. Laboratory-syphilis clinic cooperation should include:

a. Daily report sheet of all tests done on the general hospital clientele, as ell those done for the syphilis clinic sent to the syphilologist for check against clinical diagnosis.

b. Complaisance on the part of the serologist in performing clinical check procedures (provocatives, series, presumptive nd diagnostic test)

c. Complaisance in the performance of laboratory check procedures (investigation of suspicious positives, decline in sensitiveness, false positive and negative tendency adoption of improved serological procedures or those thought likely t be improvements)

7 Laboratory-practitioner cooperation should include

a. No weak positive confusing or conflicting report to be made in first instanc except as undeterminate—repeat.

b. The exception—treated cases.

c. Adequate clean specimen properly labelled, ith proper data (type of syphilis or other condition; previous treatment)

This applies with equal force to complement fixat on and precipitation procedures.

The serologic tests for syphilis have recently been subjected to heroic reevaluation. Formerly used for the examination of the sick, and to large extent those m bom some suspicion of the need for it actuated the doing of the test, the negative result as first shown to have margin of unreliability that made t unable t stand alone or thout repeated confirmation by laboratory

and clinical examination. The positive, on the other hand, received a rising vote of confidence. The past five years, the era of the Wassermann barbecue and the wholesale application of serologic tests to large groups of the well, have now shown the positive serologic test, no matter by what method or how rigorously performed, to have a margin of nonspecificity of disturbing proportions. The presence of syphilitic reagin in normal persons; its rise and fall under drugs, diseases and unexplored factors; the uncertainty as to its whereabouts, mode of generation and actual nature; its absence in undoubted syphilis with characteristic manifestations; the anxious attempts to define by such methods as verification tests, so-called, by quantitative procedures, by spirochetal antigens, including even the Reiter strain whose superior specificity approaches the ludicrous, as we have seen, all these considerations and many more have given the thoughtful observer a real case of serojitters. Imagine the plight of the practitioner, the examiner passing on Selectees, and the syphilologist, as the list of diseases (Figure 33) known to be responsible for the appearance of reaginlike substances in the blood grows and grows, and the time after their occurrence in which false tests remain positive stretches from days to years. No longer is it possible to seek refuge behind the belief that mere over-sensitiveness of test procedure is responsible for the decline in reliability of the positive report. It is true that the wholesale use of screen tests, even the best recognized of which have their slippery edges, has led to confusion, not wholly corrected by the performance on positive serums, of one of the basically more stable procedures. The trouble lies deeper than that—as deep as our ignorance of the nature and identity of the syphilitic reagin and its congeners, and that ignorance is profound indeed.

The serious search for the substances suspected of being a serum protein or globulin fraction is now on, under the auspices of the National Research Council—supported investigation, armed with chemical fractionation of plasma or serum and with Tiselli—a word to conjure with. One might suggest that the reagin may turn out to be anything but a substance—rather a relationship or variable balance or proportion between substances or fractions or a mode of reaction to varying concentrations and electrolytic conditions. But whatever it is it must now be found if we are to filter out the dross from our years of confidence in serologic tests for syphilis. How shall the practitioner in the field identify the common sense of the matter and what common denominator for the situation shall we offer him? Let us attempt one.

The Clinical Compromise.—The blood test for syphilis has always been recognized as unfit to stand alone; it is a reproach to use it as a sole basis for treatment. It cannot decide either way the question of infectiousness, ever. There, then, goes much of its public health significance. In the absence of clinical signs of syphilis, it has at most discovered only latency. That and congenital infection are, at least as we have been observing it, overwhelmingly the harvest of its routine use to determine physical status and fitness anywhere. It is strongly, repeatedly and incontrovertibly positive by any reliable or so-called "standard" method of performance early in the disease, though not quite at the start. The see-saw of weak positives and conflicting laboratory and varying method reports has been shown, subject to confirmation, to be largely "technical" stuff (Mohr and Smith 1940). It is strongly positive, or there are strong positives in a series, in asymptomatic neurosyphilis as a rule. The relatively rare exceptions are, like late tabes, brain gumma, and so on, accompanied by diagnostic signs. Liver, spleen, bone, eye, gastro-intestinal tract lesions are apt to be inescapably positive. If they are not, something is seriously wrong with the laboratory. Syphilis most likely to escape a serologic uncovering mechanism, backed by a reasonably competent examination, is that of the pregnant woman and especially the multipara, and the early cases of syphilitic vascular and cardiovascular disease. The fluoroscopic examination of the heart and great vessels and a spinal fluid examination can prevent casual misinterpretations of serologic positives or negatives, whether they represent latency or progression in the large majority of cases.

The positive diagnosis of syphilis can, then, be made safe. Its elimination once the suspicion is aroused by a test, has always been difficult, and probably will long remain so. Certainly, even with our present armament of tests and

studies roentgen-ray and spinal fluid included one hesitates to tell a person who has chalked up a strong serologic suspicion or a woman who facing marriage and pregnancy has chalked up a weak one not to take treatment They had better be treated for life insurance

In practical terms it may be said that no patient should be given his diagnosis or placed on treatment on the strength of a single positive serological test any more than on the strength of a single negative one This statement implies that there must be false positive results and these are conveniently though somewhat arbitrarily classified into technical false positives and *biological false positives*. The former being errors introduced by the intrinsic qualities of the technic or the methods of the laboratory have already been sufficiently discussed The inevitable incidence of technical false positiveness in the work of good laboratories probably ranges between 0.1 and 1 per cent Repetition to control *technical false positives should* usually be made on fresh serum but if discovered in time the original serum may also be run again provided the quantity is sufficient a a control on the repetition.

Mailed specimens, hemolysis, age (over 4 days) lack of refrigeration, bacterial contamination, cotton stoppers, improperly cleaned glassware and tubes ... alkali and other factors (Kolmer and Brown) render results unreliable

The Biological False (Non-specific) Positive Serologic Reaction.—In Fig 33 we have attempted a classification of the occurrence of biologically false positive serological reactions for syphilis, summarized from the literature and from our own experience Much of the evidence in the literature is, of

Fig. 33.

DETAIL ON BIOLOGIC FALSE POSITIVE SEROLOGIC REACTIONS

Disease group	*Frequency (estimated)*	*Duration positive*
Normal persons	1 t 4000	Temporary or permanent
	Spirochetes	
Yaws.	100%.	Persistent.
Relapsing fever	5–40%.	1–6 weeks after temperature normal.
Rat-bite fever	0–30% or more spirillary form 37 % at eptobacillary form.	While febrile
Pinta	60% early 100% late	Persistent
Bejel.	70%	
Weil' disease	Occasionally mentioned	
Field fever	100%.	
Vincent fusospirillosis.	Occasionally mentioned.	

Fig. 33.—*Continued*

Disease group.	*Frequency (estimated)*	*Duration positive*
	Protozoal Infections	
Malaria.	100% t some stage	2–4 weeks, plus.
Kala-azar	"High.	
Cutaneous leishmaniasis.	Rarely—35 cases (11 positive; 18 negat ve; remainder variable)	
Trypanosomiasis.	Unsettled	
	Rickettsial Infections	
Typhus fever / Spotted fever	Frequent.	Frequent during fever disappear in convalescence
	Virus Infections	
Vaccinia.	10–35%.	Begin bout 12 days af ter vaccination, persist until 3–4 months after vaccination. Usually low titer
Chickenpox.	Occasional	
Mumps.	Occasional.	
Measles (also Rotheln)	Occasional	
Influenza	Frequency not know	
Some respiratory infections	Frequent	Few eeks.
Virus type pneumonia?	Frequency not known.	
Poliomyelitis	2 cases	
Lymphogranuloma venereum.	0–50%, 61% rectal stricture (false?)	Fluctuating
	Streptococcal Infections	
Hemolytic strep. infections.	3 cases.	2 12 eeks
Scarlet fever	0–0.6%.	Appea 20–25 days or after 35–48 days.
Septicemia / Endocarditis.	6 of 30 cases; 16 of 32 cases 2 cases.	
Acute pemphigus.	1 case.	

Fig. 33.—Continued

Disease group	Frequency (estimated)	Duration positive
Other Bacterial Infections		
Leprosy	60–80%	
Tuberculosis.	0–0.8 to 3.7%; infantile 5%	
Pneumonia.	Occasional, up to 5–40%	Transient to several months.
Diphtheria.		
Glanders.	Mentioned.	
Ulcus molle	Denied by some; 3 of 21 cases.	
Infections Cause Unknown		
Infectious mononucleosis.	2–20% 5–10% (Rein) 20–63% (Moore)	5 months.
Sore throat, no organism.	9 cases.	
Pulmonary	Occasional.	
Acute abdominal infections.	Occasional.	
Urogenital infections.	Occasional.	
Acute adenopathies.		
Dysentery Amoebic?	1 case 1 case	
Fever	2.2–8.9%.	
Acute lupus erythematosus.	Occasional.	
Sarcoidosis.	Occasional.	
Metabolic and Nutritional States		
Hyperproteinemia.	25%.	
Scurvy Purpura Acute malnutrition (infants) Cardiac disease Pellagra Beriberi	Isolated cases.	

Fig 33 —*Continued*

Disease group	*Frequency (estimated)*	*Duration positive.*
	Malignancy	
	1.6–9 7% 0–21.5% Standard tests nearly all 100% specific.	
Carcinoma of cervix.	14.1%.	
Leukemias.	Occasional	
Granuloma fungoides.	Occasional.	
	Drugs	
Arsphenamines.	Occasional.	
Lead poisoning	Occasional.	
Ether anesthesia narcotics, alcohol, paraldehyde etc.	About 20%.	Lasts up t 14 days.
Acetic acid poisoning.	Occasional	
	Miscellaneous	
Jaundice	2 0–3.9%.	
Pregnancy	0.5 to 1.9–3.8%.	
Epilepsy (?)		
Coronary thrombosis (?)		
Horse serum therapy (?)		
Cadaver blood Various diseases Psoriasis Pemphigus Aphthae (herpes) (see virus) Basedow disease Diabetes (?) Eclampsia Ulcus tropicum		
Menstrual blood (?)		

course dependent on individual cases, for extensive surveys are comparatively rare Certain conditions, notably frambesia, trypanosomiasis, ulcus tropicum and recurrent fever are comparatively rare within American territory or jurisdiction but will become more significant because of the war Admiral Stitt has pointed out that he *believes a part of the reported evidence*

for nonspecific positive Wassermann reactions in lepra comes from patients who have been cross-infected with yaws. Several illustrations are included among the case summaries in this chapter (Figs 31 35 30) There is not the slightest doubt in our minds that by the older Wassermann procedures and, on occasion, also by both the modernized Wassermann procedures and the precipitation tests, unquestionable nonspecific positives are obtained in chronic occult glandular tuberculosis, endocarditis subacute septicemic conditions and the cross fire of the two types of process which one observes occasionally in patients with "tuberculids" "septids" and the septic phase of disseminate erythematous lupus.

Fig. 31.

SEPTIC FOCUS? FEBRILE STATE, PROBABLE NONSPECIFIC POSITIVE SEROLOGICAL TESTS QUESTIONABLE EVIDENCE OF SYPHILIS

Youth, aged seventeen.

Chief Complaint Supposed acute appendicitis with fever hurried to hospital.
Routine Blood Wassermann Reaction by hospital laboratory no clinic control, strongly positi
Fever Subsid s, patient discharged, no operation.
Kolmer, 00, Kahn 014, four days after first bismuth injection, hile patient afebrile. Clinic-controlled laboratory
Immediate and Subsequently Repeated Tests, totally negative
History of running y from home t weeks t age fourteen. Denies exposure probably truthful.

Previous Bouts of Fever hes exerac ti e, recovers in bed.
Physical Examination Heavy clavicles, slightly rounded tibia, otherwise negative. Basal erosion, angle of mouth, disappears after first injection Bi. Mother serologically and superficially clinically negativ
One Year' Treatment, no change physically Serologically constantly and completely negative. Lapsed from observation.

Discussion

1 Improbable though not impossible that this patient has syphilis.
2 Unsupported single positive blood Wassermann reaction during febrile interlude not sufficient to make diagnosis.
3. Mouth erosion hile not suggestive in appearance might have had darkfield even then might have given erroneous findings.
4 Could the blood W ssermann reaction have been so completely reversed four days after half dose of B' if dealt syphilis? Probably not.
5 A prenatal infection or an acquired infection three years old ith mucosal relapse (previously untreated) ould almost certainly ha been more resistant serologically
6. This is probably therefore nonspecific positive blood W ssermann reaction associated with febrile period, cause unknown.

The True Positive Serological Reaction.—The preceding discussion of the pros and cons of positive serological results must not be allowed to dim the realization in the mind of the practitioner of the very high diagnostic value of the positive blood serological reaction. For this reason the person who has had a single unconfirmed positive Wassermann test must at least be enjoined to have the test repeated at some interval too short to permit of damage, and yet long enough to allow of a change in the complement-binding qualities of his serum.

Summaries of adequate procedure are given in Fig 57 and "The Clinical Compromise under Clinical Aspects

Fig. 35.

SEPTIC PEMPHIGUS? OR ACUTE DISSEMINATE LUPUS ERYTHEMATOSUS WITH BIOLOGICAL FALSE POSITIVE (NONSPECIFIC) SEROLOGICAL TESTS

Rabbi, aged thirty, married.

N Children, no miscarriages.
Examined 9/6/31
8/31 "Grippe."
Followed by profuse bullous eruption with crusting and erosions, face, scalp, chest, flexures. Multiple erosive mouth lesions. Papula axillary and perineal lesions.
Darkfield **Negative.**
N Fever
9/8/31 **BWR, Kolmer 44, Kahn 122, and Kline Positive.**
Extension of **Lesions**, no hoarseness.
BWR Three Weeks Later Kolmer *22*, *Kahn 122*, *Kline negative.*
Blood Count, slight leukopenia (4350 WBC)
N Clinical or Familial Evidence of syphilis, acquired or prenatal.
Bismuth and Bismuth Arsphenamine Sulphonate Intramuscularly N Effect.
10/31 **Extensive Severe Sepsis,** impetiginous, paronychial and whitlow lesions.
Fever to 103 F
No blood cultures (out of control)
Vegetative lesions ppea
10/31 **Death.** No autops

Discussion

1 This patient almost certainly did not have syphilis. The serological tests were done in conservative laboratory under clinic control.
2. This is probably clinical example of th septicemic (butcher's) type of pemphigus, though it also suggested the septic phase of acute lupus erythematosus.
3 It illustrates how septic process with fever may yield probably false positive results in both complement fixation and precipitation test for syphilis

Fig. 36.

FEBRILE PSEUDOSYPHILIS AND THE CONFLICTING SEROLOGICAL REPORT

Male, aged forty-eight, married.

Examined 11/13/28.
Wife and 2 children ell, no mortality
8/28 "Grippe, fever 100 t 101 F
Lump Below Jaw Supposed carbuncle (Had had t previously)
History of "Cut" by Barber no sequela
9/28 **Loss of Weight,** malaise
10/28 **BWR Positive,** *State laboratory*
BWR N gative, excellent privat labora tory
BWR Positive, on repetition by same private laboratory
10/28 ***Skin Eruption,*** *called purpura by internist.*
BWR Positive by Third Laboratory ith- out clinical control.
Systolic Aortic Murmur First Heard. No enlargement.
Widal, blood cultures negative.
11/28 **Patient Continues Mildly F brile.**
Treatment for Syphilis Begun with Neo.
Eruption Disappears.
Fever Continues, with occasional evening chills.
11/28 **General Health Improves.**
BWR Strongly Positive by Third Laboratory (as above) again obtained after sixth injection Neo.
BWR Kolmer 11, Kahn Negative, Hinton Negative **Kline N gative** by fourth laboratory (syphilis clinic-controlled).
N Clinical Evidence of Syphilis acquired or prenatal Mother has had miscarriages.
N Exposure in many years.
12/28 to 12/29 **Treatment Continued.** Fever slowly subsides Occasional evening chills
Murmur unchanged.
Kolmer Kahn, Hinton, and Kline tests continuously and completely negative.

Discussion

1 A classical series of serological conflicts, probably on nonspecific basis in patient who probably had transient febrile, possibly septicemic condition ith recovery
2. Treatment for syphilis was carried through because it was impossible to decide absolutely whether the patient had had syphilis or not.

Fig. 37

THE CHECKING OF A POSITIVE SEROLOGIC TEST REPORT*

1. Condition of mailing, receipt, elapsed time, hemolysis, stoppers, etc.
2. Who performed the test?
3. What procedures used? Standard
4. How strongly positive? Can a titer be obtained
5. When was the test performed in relation to the biologic background of the person: menstruation, intoxications, fever, intercurrent acute infection, other chronic infections, subacute bacterial endocarditis, anesthesia, alcoholism?
6. Any malaria, lepra, yaws, tuberculosis, bacteremia. Review Fig. 83.
7. Result on repetition
   a. By same laboratory on original specimen if still available and on fresh specimen
   b. By an approved check laboratory (United States Public Health Service standard)
   In series or after an arsenical or bismuth provocative effect (suspected of nonspecificity)
8. Result of a physical examination of the patient.
9. Result of the epidemiologic (contacts and family) inquiry. Go as far as you can.
10. The history of infection (30 per cent to 60 per cent margin of error and almost worthless in women)
11. The spinal fluid examination—if case weighs "50–50" or in opinion of an experienced referee or consultant.
12. Observation—invariably if case weighs "50–50," often even if not (six months to yearly)
13. "No case intuition—a factor in expert decision
14. Treatment on suspicion. Response of symptoms may be nonspecific of tests, unreliable. Do not treat genital lesions on suspicion, merely to observe response. "On suspicion" really should usually amount to the same thing as treatment appropriate to positive diagnosis.

Moore and his associates* have suggested the following procedures when biologic false positive serologic tests for syphilis are suspected: Careful history; careful physical examination for evidences of acute infection preceding the questionable serologic test, with special reference to lymph nodes, spleen and lungs; search of blood smears for malarial parasites; blood smears for infectious mononucleosis; blood test for heterophile antibody (the Paul-Bunnell test) which is specific for infectious mononucleosis; determination of the sedimentation rate; repetition of the serologic test for syphilis by several different technics and in several different laboratories; performance of a verification test; testing the patient's serum by complement fixation with spirochetal antigen; testing the patient's serum with wholly nonspecific antigens such as those prepared from bacteria; prolonged serologic follow-up; examination of the members of the family and sexual contacts; examination of the cerebrospinal fluid, if decision cannot be reached earlier. These authors consider the provocative procedure worthless. They advise withholding antisyphilitic treatment unless and until the diagnosis of syphilis is proved.

* Stokes, J. H. Amer. J. Syph. Gonor. and Ven. Dis. 23:349, 1939. Moore, J. E., Eagle, H. B. and Mohr, C. F. J.A.M.A. 115:1602, 1940.

The highest positive efficiency of the blood serological tests is reached in the period extending from about three weeks after the appearance of the chancre to the height of secondary manifestations, covering roughly about six months. From this pinnacle of efficiency the proportion of positive serological results obtained from the blood gradually declines.

The percentages expressing this decline in efficiency vary substantially with different writers and are a function of three factors, the last of which is too often forgotten. The first factor is the delicacy of the test, as performed in the laboratory; the second is the treatment which the patient has received, and the third is the amount of clinical skill and judgment applied in the clinical examination in conjunction with the test to recognize those cases which fail to yield positive

serological results. Many of the high proportions of positive serological tests reported in latent recurrent and late syphilis are the result of serological rather than combined serological and clinical diagnoses in which the positive test itself rather than the clinical manifestations of the disease, constitutes the proof of the presence of syphilis. The proportion of initially blood serologically negative syphilis can be considerably increased and the positive group correspondingly diminished by the use of multiple clinical procedures for identifying the disease without the aid of positive blood test and by the systematic employment of the Wassermann series. The provocative procedure is unreliable Certainly it is out of the question to accept as conclusive opinions hich are based largely on the serological material sent to laboratories with the presumption of syphilis raised by the less critical judgment of general medical men. Inasmuch as it sometimes takes a pretty obvious and hence probably serologically positive syphilis to arouse suspicion, such results may read high in the proportion of positive t negative.

As examples of the extremes in estimation hich are current, Craig summary in latent syphilis quotes Grosser as obtaining 83.3 per cent positives by complement fixation technic, while Vedder gives 80.7 per cent. Craig own results yield 68.1 per cent. Fordyce, in 881 late cases, obtained 72.3 per cent positive reactions on the blood The results obtained with complement fixation procedure in the Mayo Clinic on 252 cases of untreated syphilis summarized b Des Brisay are given in Fig. 38

Fig. 38.

PERCENTAGE OF POSITIVE BLOOD WASSERMANN REACTIONS IN TYPES OF UNTREATED SYPHILIS (252 CASES)

	Cases.	Positive.	Per cent.
Visceral	18	18	100 0
Latent	49	46	93 8
Cardiovascular	20	17	85 0
Osseous	19	16	84 2
Cutaneous	22	18	81 2
Mucous membrane	10	8	80 0
Neurosyphilis	114	47	41 2

Des Brisay Mayo Clinic

These figures, while obtained largely from one of the older serological technics, illustrate very clearly the difficulty of estimating the frequency of positive reactions in an aggregate including all types of syphilis Neurosyphilis stands out in this series in a way which suggests almost an inherent trend toward serological negativity on the blood On the other hand it must be remembered that neurosyphilis is the symptomatic syphilis of internal medicine and that diagnosis can frequently be made by signs quite irrespective of serological findings. On the other hand, in visceral syphilis, where the disease is almost never even suspected unless the routine serological tests indicate its presence it is to be presumed that 100 per cent of positive serological tests will be obtained Cardiovascular syphilis often quite as important as neurosyphilis as a source of diagnostic error associated with negative blood serological tests, stands comparatively high in the list of positive Wassermanns because it is so largely diagnosed by the blood findings rather than the clinical examination

Using the older serological technics, Stokes and Brehmer found, in 200 railroad men and farmers, as they entered the Mayo Clinic, an incidence of positive blood Wassermann reaction of 42 to 50 per cent. In 200 syphilitic patients hose chief complaint was "stomach trouble, large proportion of whom had neurosyphilis, Brown and Stokes found 43.5 per cent positive blood Wassermann reactions. Des Brisay succeeded in demonstrating, in his series of cases, the spontaneous decline of the proportion of posit ve serological tests through the years of duration of the ordinary syphilitic infection, beginning with the positive blood and spinal fluid

through the negative blood and positive fluid and finally to complete serological negativity with lapse of time

The more distinctly modern figures based upon the Kolmer modification of the Wassermann test, are given in Fig. 39 The same considerations, of course apply to some extent to a table of this sort, with reference to the relative weight of clinical and serological diagnosis but certainly these figures satisfactorily indicate the serological expectancy of a positive test as performed today in one of the best laboratories of the world Again however in cardiovascular and neurosyphilis we believe that the proportion of seronegative cases would be higher if clinical diagnosis could be stepped up to its maximum efficiency In general the more acute the clinical judgment exercised and the more the collateral means for proving syphilis are used the lower will be the percentage of positive blood serological reactions in the syphilis which is diagnosed.

Fig 39

INCIDENCE OF POSITIVE KOLMER WASSERMANN REACTIONS IN VARIOUS TYPES OF SYPHILIS

Type of syphilitic involvement.	Blood Wassermann positive, per cent.	Spinal fluid Wassermann positive per cent.
Primary 5–14 days	41	
10–14 days	73	
3– 4 weeks	84	
4– 6 weeks	91	
Secondary	99–100	
Latent (men)	90	
(women and children)	50– 80	
Chronic skin and mucous membranes	90– 95	
Bones and joints	80– 95	
Gastric	80– 85	
Liver and spleen	90– 93	
Cardiovascular	80– 98	
Ear nose and throat	70–100	
Iritis	100	
Prenatal latent	40	20– 40
Prenatal skeletal	70	
Interstitial keratitis, iritis, choroiditis, etc	90– 93	
Neurosyphilis, asymptomatic, (early)	83–100 (in early [illegible])	20– 40
Asymptomatic (late)	70– 90	80– 90
Tabes dorsalis	70– 85	96
Primary optic atrophy	83	93
Paresis	98–100	100
Cerebrospinal	80– 90	93–100

A tabular summary of the sensitivity of current serologic tests based on the "early-late" type of chronology much used in public health work is given in *Fig. 40*

The Effect of Treatment on Serological Reactions.—Treatment for syphilis has the general effect of reducing serological tests from positive to negative The degree to which such an effect is obtained is, of course dependent on a number of factors, including the amount and kind of treatment, the character of the infection, its duration and so forth. It is a comparatively easy matter to reverse serological reactions in the first few weeks of the infection It

Fig. 40.

SENSITIVITY OF VARIOUS SEROLOGIC TESTS IN TREATED AND UNTREATED CASES OF SYPHILIS*

Name of test.	Early untreated primary and secondary (45 cases)	Less than 4 years receiving varying amounts treatment (119 cases)	Over 4 years, treated and untreated (approx. 218 cases)
	Complement Fixation		
Boerner Lukens, simplified.	82 2%	55 9%	79 5%
Eagle Wassermann.	83 0%	46 3%	61 6%
Kolmer simplified.	91 1%	59 7%	78 6%
	Flocculation		
Boerner-Jones Lukens, simplified micro.	81 1% 84 4%	51 3% 55 8%	65 6% 71 9%
Davies-Hinton micro.	88 9%	61 4%	86 3%
Eagle	83 5%	57 2%	78 1%
Hinton.	73 6%	47 1%	74 1%
Kahn, standard.	86 7%	51 2%	63 1%
Kline diagnos. micro.	71 6%	50 1%	67 9%
Mazzini slide	83 6%	60 1%	87 5%

* Extracted from Preliminary Report Washington Serologic Conference 1941 Ven. Dis Inf., 23 161, 1942

Fig 41.

SEROLOGIC RELAPSE AND BLOOD SEROLOGY IRREVERSIBLE (WASSERMANN FASTNESS) OBTAINED IN THE COOPERATING CLINICS, BY DIAGNOSIS ON ADMISSION

Diagnosis of early syphilis.	Serologic relapse, per cent.	Blood serology irreversible (Wassermann fast). 1 Year per cent.	Over 1 Year per cent.
Seronegative primary	6 4	1 2	2 6
Seropositive primary	9 9	7 5	7 0
Secondary (first year)	10 7	5 5	7 8
Secondary (Delayed)	10 8	7 7	13 6

Adapted from Table 14 Cooperative Clinical Studies in the Treatment of Syphilis, Ven Dis. Inf., 1932.

becomes exceedingly difficult where the disease had been literally bred into the bones and tissues of the patient, as in prenatal or congenital syphilis. Moore and Kemp after Keidel and Moore had paved the way by years of routine weekly serological tests on all patients under treatment for syphilis were able to show very beautifully the gradient of serological decline from positive to negative in early syphilis and its relation to the type of treatment administered. While this will be more fully discussed later their composite figure is reproduced here to show the average rate of decline of the Wassermann reaction from strongly positive to weakly positive and finally to negative under treatment, and the tendency of the curve to become positive even though originally negative when treatment is allowed to lapse (*i. e.*, is intermittent instead of continuous) Fig 41 illustrates in terms of serologic relapse and irreversibility the principle that so far as treatment effect on blood serology is concerned, seropositive primary syphilis should be classified with secondary rather than as primary syphilis.

The behavior of the serological reaction under treatment is by no means always according to schedule. In the later phases of the disease as well as in asymptomatic latency reversals to negative may be accomplished with almost unbelievable ease and again, *pari passu*, the seemingly most eligible case, ideally handled, may obstinately refuse to show serological response. Patients may undergo an easy and early reversal to negative only subsequently to become positive again during a rest interval or lapse thereafter to remain irreversibly positive indefinitely On the other hand a serological reaction may be only weakly positive at the outset, to become strongly so after treatment is initiated, to remain strongly positive throughout the entire course of treatment, even over a period of years and then, without explanation, to become promptly or slowly negative and to remain so after treatment has ceased. There is often a definite lag between the administration of treatment and the securing of serological effect. This is seen in nonspecific therapeutic methods, such as fever therapy in which there is no necessary parallelism between clinical improvement and serological response, though satisfactory serological response may be secured months or even years after the administration of the critical treatment in the case Reference has already been made to the spontaneous gradient of decline demonstrated by Des Brisay in our serological results in untreated syphilis Beerman (1939–42) summarized his own and other observations on the retarding, "lag" effect of bismuth on blood serologic reversal when used in simultaneous combined treatment in early syphilis, with the arsphenamines and mapharsen.

Serological response varies not only with the treatment and characteristics of the individual case, but with the method of measurement, or testing employed. Thus it may be legitimately urged with respect to a given serological procedure that its delicacy is appropriate to treatment while inappropriate to general diagnosis In other words, it has a distinct tendency to give false positives which are less serious when obtained in a treated case because they merely result in a perhaps harmless or even desirable prolongation of treatment, while they are extremely undesirable in undiagnosed patients on account of the risk of fastening a diagnosis of syphilis upon a person who does not have the disease.

The Fixed Positive Blood Serological Reaction (Sero-resistance, Reaginfastness).—Serological reactions for syphilis which will not become negative under treatment are spoken of as fixed, irreversible or resistant *positive*

Fig. 48.

CURRENT USES FOR AND VIEWS ON QUANTITATIVE BLOOD SEROLOGIC TESTS

1 Still relatively esoteric procedure not easily available without exceptionally high grade f usually noncentralized laboratory service (so far available routinely in only one stat) The so-called "Vernes syphilimetry widely used in pre-W France an early example
2. Of littl value in diagnosis as yet except in congenital syphilis.
3. Of most significance in treatment best studied nd most useful in early syphilis, and in the kild of a syphilitic mother
4 Usually conducted as reagin titer estimation. For comparable results all test must be run in the same laboratory (Moore and Eagle 1941)
5. When thus empl yed, it ppears that
   Wide variations in reagin titer ppear (0 t 1600 units) Titer tend t ru t higher levels in early than in lat syphilis.
   b These variations appear even in infections hich are otherwise linically similar in manifestations and intensity
   Titer is however generally lower in primary tha m secondary syphilis
   d It is initially lower and falls more rapidly under treatment in clinically mild (few isolated lesions) secondary syphilis than in florid" extensive secondary syphili (Crosby nd Campbell, 1941)
   In early syphilis (Moore and Eagle series) the primary syphilis mean as 104.3 plus-minus, 13 74 units, media 43.2 plus-minus 17 92 units; the secondary syphilis mea w 179.6 plus minus, 7.54 units; median 142.5 plus minus 9 45 units.
   f In late syphilis (same uthors) there are no correlations bet een the type or gravity of the involvement and the serologic titer The range is from 0 t 1600 units, the mean titers of the five groups or types of involvement ranging from 21 5 t 44 1 units. Late latent and tabetic neurosyphilis tend t have lower titers.
   g Reagin titer though educed by treatment in late syphilis not guide to the lessening of gravity of the infection or t clinical improvement under treatment.
   h. Reagin titer does not increase in proportion t the duration or completeness of the latency It is not direct expression of the degree of immunity or resistance t infection.
6. Used as measure of effectiveness, reagin titer indicated that five arsenicals commonly used in treatment of early syphilis did not differ materially in their bility t lower the titer Moore and coworkers (1936) concluded this was insufficient evidence to prove equal all round effectiveness.
7 A sudden rise in reagin titer may presage relapse in early syphilis (Kahn, 1930).
8. A rise in titer in the blood of the child of syphilitic mother in serial examinations post partum indicates the presence of the infection (not merely carry-over from the mother blood)
9 Working with fever alone and with combined fever and hemotherapy Simpson, Rose and Kendell (1942) showed (Kahn quantitative procedure) that
   a. Th lower th initial titer in early syphilis, the more rapid the reversal t negative
   b A provocative effect is observed at the institution of treatment in some cases (observed but discounted by Crosby and Campbell, 1941 in seronegative primary syphilis) Possible lag effect.
   In primary syphilis treated twice weekly serologic reversal required from twenty three t sixty-four day depending in part on the titer at the outset in secondary syphilis treated once weekly fifty to ninety-three days; in secondary syphilis treated twice eekly in twenty-eight t sixty-six days. The uthors conclude however that semiweekly treatment has no advantages over weekly treatment the rat of reduction being dependent on the original titer
   d. The results of single f ver-chemotherapy session in primary syphilis ere essentially the same as for multiple sessions.
10. In patients with persistent seropositiv reactions or delayed reversals, under treatment, reagin titer methods may show favorable progress (decline) or unfavorable progress (increase) hen ordinary test indicat simply persistent positive reaction (Kahn, Simpson, et al)

Fig 42.—Continued.

11 Ninety-nine per cent of th bserved extreme titer rang (1 t 5400 units) falls in the classification of "strong positive or 4 plus" by ordinary nonquantitative procedure
12. The original dictum of Wile and Hasley deserves remembering—the more sensitive the procedure (i.e. detection of minut amount of reagin) the farther i the serologic "cure of syphilis removed; and it may be added, illustrated by Crosby nd Campbell, the less serongative primary syphilis there is.
13. Quantitative procedure is of great importance in prognostic and therapeutic study of the spinal fluid (see prognostic types) and Kahn (1939) emphasizes reagin content of spinal fluid control of treatment effect.

reactions. Again the interpretation of the phenomenon must vary with the amount of treatment, the character of the disease in the patient and the methods of testing employed.

In all probability w shall never fully understand the significance of the irreversible positive until the source of the Wassermann antibody is definitely known. If it comes from minute obscure focus of spirochetes, perhaps in an insignificant location, the reagin being the product of the breakdown of the organisms, the interpretation of the fixed-positive patient situation must

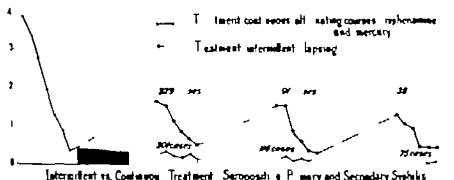


Fig. 43.—The Wassermann "gradient of reversal from strong positive (4) t negative (0) in early syphilis under treatment. The upper line (succession of peaks) represents the relapses t positive under intermittent treatment in contrast with the steady fall to negative under continuous treatment. (From Moore nd Kemp, Bull. Johns Hopkins Hosp Vol. 39 1926 Published by Williams and Wilkins Co.)

be somewhat different from that which ould prevail if the irreversible positive could be regarded as permanent metabolic change in those previously infected with syphilis but perhaps no longer harboring the organisms. In the former the positive test means active defense, organisms in process of destruction. In the latter case one could think of the positive serological test as species of scar which could be regarded as of no importance. The possible interpretation of the Wassermann reagin as an agent in the defense mechanism ould make the retention of positive Wassermann almost theoretical desideratum in certain cases.

There is not a little evidence to suggest that a positive serological reaction is by no means necessarily disadvantageous *ipso facto* Some of the gravest forms of syphilis carry the patient on to dissolution with absolute and continuous serological negativity while some of the most harmless and most protracted latencies seem to be accompanied by absolutely irreversible positive blood serological reactions (the miliary type of focal defense à la Warthin)

Definition of a Fixed Positive Reaction.—While it is impossible to define precisely what a fixed positive blood serological reaction is, one may say roughly for purposes of discussion, that it is a blood serological reaction which remains positive after twenty or more intravenous injections of an arsphenamine given in combination with twenty weeks of intramuscular heavy metal therapy with either bismuth or mercury or both. Serological tests may be regarded as persistently positive under these circumstances, even though there may have been a brief interval in which the intensity of the positive phase was apparently reduced or rendered fluctuating by the treatment. Even though such cases are reduced to negativity by prolonged *and intensive treatment, they tend to become positive again* at once upon the cessation of treatment and at times even to gain in positive intensity from a comparatively mild positive at the start to a strong positive at the close of treatment. The first concern, in the interpretation of pictures such as this, is the possibility of an underlying cardiovascular or neurosyphilitic complication unrecognized in the ordinary management of the case. A fixed positive blood serological reaction automatically raises the question as to whether the spinal fluid has been examined. If this has not been done, it *must* be done before any real interpretation of the findings or the proper course to pursue can be made. Similarly the presence of a resistant positive blood serologic reaction in a patient under treatment always demands a painstaking physical examination of the cardiovascular mechanism. Unfortunately the signs of cardiovascular change in such cases may be equivocal or wanting. It is then only possible to tell the patient that repeated examination over a period of years is absolutely necessary to the interpretation of the situation. In our more recent observations, it has seemed that the blood serological reaction in an obscure and gradually developing subthreshold cardiovascular syphilis tends toward frequent periods of transient negativity, fluctuations in positive strength and ultimately to a complete negativity some time after treatment is discontinued while the cardiovascular lesion continues its slow progress. This is perhaps particularly true of the early case and less in the later fully developed case in which definite physical signs can be recognized.

In some cases a liver slightly enlarged, a palpable spleen, obvious general enlargement of the lymph nodes, may provide a suspicion as to the reservoir of infection which is maintaining the serological positive. On the other hand, all signs or suggestions as to a physical site may be absent and the disease may present itself to both patient and physician merely as a positive serological test. It can never be overemphasized that the prolonged and intensive treatment of a patient whose only evidence of the disease after most painstaking examination, is a positive serological test on the blood, is a matter requiring the most discriminating judgment and painstaking consideration and that it is at the present day more over than underdone. This question is more fully discussed and the guiding principles to be used are presented in the discussion of treatment in latency.

The Too-Readily Reversible Positive Serological Reaction.—Moore and Kemp (1926) succeeded in showing that in early syphilis at least, those patients who fail of a sufficiently prolonged or at least a typical degree of serological resistance and who become serologically negative in a very short time have apparently a distinctly more marked tendency toward relapse. This easy reversal of the blood serological reaction accordingly becomes a trap for the unwary physician in the early treatment of the disease and a means by which

infectiousness is perpetuated through the too-early discontinuance of treatment and through ill-advised assurances to the patient regarding his supposed noninfectious condition while serologically negative It may be considered a rule of thumb that the patient under standard treatment with an arsphenamine and a heavy metal whose serological reaction reverses to negative before

Fig 44.

PROCEDURE FOR THE PHYSICIAN DESIRING INTERPRETATION BY MAIL OF BLOOD SEROLOGIC REACTIONS*

He should supply the following information for questions on serologic test involving patient or patient-type

1 Age sex, marital and family status of patient.
2. Contact and exposure data.
3. Adequate clinical examinations reported in detail, conforming approximately to the schedule i Chapter 11
4. Who did the serologic test?
5. What methods were employed, and what checks?
6 Result of repetition and by whom performed.
7 With reference t intercurrent factors relating t false positives including:
   a. Residence in tropics and so forth (malaria, lepra, y)
   b. Intercurrent infectious disease especially tuberculosis and streptococcal infections.
   Fever of any kind.
   d Relation of test t pregnancy menstruation, and delivery
8. Previous treatment for syphilis and effect on tests.
9 A satisfactory report on a completely and properly performed spinal fluid examination.
10. Results of investigation of the family

On serologically fast cases the following special information is essential

1 Time in the infection that treatment was begun.
2. Total number of arsenical and heavy met l treatment received.
3. Information on dosage employed.
4. Over how long total period was treatment spread
5. A schedule indicating the grade of irregularity if any
6. Time in the course of treatment that most irregularity appears.
7 Report of an adequat spinal fluid examination.
8. Physical status of the case both as of the present, nd if possible, at the time infection was acquired.

The doctor get poor nswer because he gives no history of the case in serologic fast questions (81 per cent); gives no clinical data (40 per cent); provides no spinal fluid examination report (81 per cent). Avoid short-cut tests.

Comment

1 Do not ask questions about serologic-fast case ithout providing or arranging for a complete and accurat spinal fluid report.
2. Scrutinize the false positive as closely as the negative including biologic as well technical possibilities of error
3. Laboratories creat confusion by reporting eak positives t any but experts.
4 Much trouble with serologic results under treatment comes from rest periods, lapses, irregularity in early treatment

* From "8,000 Questions the Doctor Asks About Syphilis"—Stokes, Ingraham and Stannard Ven. Dis. Inform 21 147 1940.

the eighth week of his treatment, is showing a positively dangerous degree of serological response and one which predicates a distinct tendency to relapse or to continuance of the syphilitic process under the cloak of a negative serology A reversal to negative in an early case nearer the sixteenth than the eighth week, provided the negative persists, is of favorable rather than unfavorable significance for the ultimate outcome

Definition of a Fixed Positive Reaction.—While it is impossible to define precisely what a fixed positive blood serological reaction is, one may say roughly for purposes of discussion, that it is a blood serological reaction which remains positive after twenty or more intravenous injections of an arsphenamine given in combination with twenty weeks of intramuscular heavy metal therapy with either bismuth or mercury or both. Serological tests may be regarded as persistently positive under these circumstances, even though there may have been a brief interval in which the intensity of the positive phase was apparently reduced or rendered fluctuating by the treatment. Even though such cases are reduced to negativity by prolonged and intensive treatment, they tend to become positive again at once upon the cessation of treatment and at times even to gain in positive intensity from a comparatively mild positive at the start to a strong positive at the close of treatment. The first concern, in the interpretation of pictures such as this, is the possibility of an underlying cardiovascular or neurosyphilitic complication unrecognized in the ordinary management of the case. A fixed positive blood serological reaction automatically raises the question as to whether the spinal fluid has been examined. If this has not been done it *must* be done before any real interpretation of the findings or the proper course to pursue can be made. Similarly the presence of a resistant positive blood serologic reaction in a patient under treatment always demands a painstaking physical examination of the cardiovascular mechanism. Unfortunately the signs of cardiovascular change in such cases may be equivocal or wanting. It is then only possible to tell the patient that repeated examination over a period of years is absolutely necessary to the interpretation of the situation. In our more recent observations, it has seemed that the blood serological reaction in an obscure and gradually developing subthreshold cardiovascular syphilis tends toward frequent periods of transient negativity, fluctuations in positive strength and ultimately to a complete negativity some time after treatment is discontinued, while the cardiovascular lesion continues its slow progress. This is perhaps particularly true of the early case and less in the later fully developed case in which definite physical signs can be recognized.

In some cases a liver slightly enlarged, a palpable spleen, obvious general enlargement of the lymph nodes, may provide a suspicion as to the reservoir of infection which is maintaining the serological positive. On the other hand, all signs or suggestions as to a physical site may be absent and the disease may present itself to both patient and physician merely as a positive serological test. It can never be overemphasized that the prolonged and intensive treatment of a patient whose only evidence of the disease, after most painstaking examination, is a positive serological test on the blood is a matter requiring the most discriminating judgment and painstaking consideration and that it is at the present day more over- than underdone. This question is more fully discussed and the guiding principles to be used are presented in the discussion of treatment in latency.

The Too-Readily Reversible Positive Serological Reaction.—Moore and Kemp (1926) succeeded in showing that in early syphilis at least, those patients who fail of a sufficiently prolonged or at least a typical degree of serological resistance and who become serologically negative in a very short time have apparently a distinctly more marked tendency toward relapse. This easy reversal of the blood serological reaction accordingly becomes a trap for the unwary physician in the early treatment of the disease and a means by which

test. Greenbaum, in an interesting study of 100 cases, was able to compile 50 examples of diagnosed syphilis which gave positive Kahn tests and negative Wassermann tests, and a like number which gave positive Wassermann tests and negative Kahn tests. Houghton *et al.*, however reported 76 positive Kahn reactions when the Wassermann was negative out of 40 cases, against 21 positive Wassermann reactions with negative Kahn tests out of 16 cases, all the patients having undoubted syphilis. Walker in 181 cases of diagnosed syphilis, reported all Kahn reactions positive while only 107 gave positive Wassermann reactions, 43 moderately positive reactions and 26 negative. Berry Ey and De Long in 363 cases in the various stages of syphilis, found that 256 gave positive Kahn reactions and negative Wassermann reactions while only 27 gave positive Wassermann and negative Kahn reactions.

The more recent advocacy of multiple tests of differing types is well presented by Boerner Lukens and Gilman (1938) who found three tests yielding the highest proportion of positives; and Schoch (1939) who recommends five tests under clinic control.

It would appear therefore, that the examination of the blood of a seronegative patient by a precipitation reaction, especially if some of the older Wassermann technics have been used to obtain the original negative is an essential part of the interpretation of the negative serological reaction.

Where a particular type of syphilis is suspected in the patient, but the serological result is negative it cannot be said at the present time that any one test procedure should be invoked for reinterpretation. The results of various observers are too conflicting and the advantage of any particular test too small to permit of any other generalization than that two or more test methods, including a complement fixation and a precipitation technic, should be employed

Danger of "Stepping Up" Sensitiveness of Tests.—Every attempt to reinterpret the negative by stepping up the sensitiveness of the procedure used, is fraught with a very definite element of danger from nonspecific effect. This applies, for example as Kolmer points out, to the reading of the Kahn test after refrigeration instead of at the completion of the reaction as required by the standard procedure. From such intensification including the use of highly cholesterinized antigen, serious trouble is sure to ensue except, perhaps, in the interpretation of known syphilis under treatment. The proper place for the sensitive procedure in eliminating false negatives is at the beginning of a study of any patient's serum rather than at the end. It is more important, in the main to eliminate false positives than false negatives.

Serial Testing and the Provocative Procedure.—As in the case of a suspected false positive, the suspected false negative may be tested by serial repetition, the number varying with the circumstances of the case

While the original provocative which consisted of a series of daily serologic tests following a single injection of an arsphenamine, has lost much of its significance through the study of nonspecific reaction previously referred to, there still remains a residue of usefulness in the procedure which should not be wholly discarded. Most of this residue resides in the worth of a series of tests as distinguished from a single test. On the other hand there is sufficient accumulated evidence from Gennerich in 1910 to current experience, to indicate that a rise in reagin titer both in the blood and spinal fluid does follow the use of antisyphilitic treatment in syphilitic persons, and that this may have some confirmative value in the more complex groups of procedures required for diagnosis in doubtful cases. The decreasing use of the provocative is due partly to fear of therapeutic shock effect of stirring up the disease, if it is present, without continuing treatment to the practical difficulties of daily blood-tests and the expense of their performance to the now well

recognized fluctuation in the daily serologic results even of the best laboratories and to the nonspecific possibilities mentioned Probably the most useful form of provocative procedure in our experience at least is the repeated injection of a bismuth compound at weekly intervals for four or five injections with serologic tests performed simultaneously with each injection. Such heightened positiveness as appears occasionally assists materially in confirming the belief that a patient who would ordinarily fall in the category of doubtful is actually the victim of a syphilitic infection By such a method there is little or no danger of therapeutic shock, and if the result is well defined its confirmatory value is often gratifying Quantitative procedure can be invoked in this method and a titer below four units of reagin may justifiably be regarded at the height of the test as uninterpretable.

Fig 45

CERTAIN POSSIBLE COMBINATIONS WITH THE NEGATIVE BLOOD SEROLOGIC REACTION

A negative blood serologic reaction may occur with

1 A positive darkfield, both early and late.
2. Secondary syphilis, especially treatment resistant
3. An active cutaneous late syphilid
4. An active bone lesion, especially of the palate and clavicle
5. *Spirochaeta pallida* in the blood.
6 A positive spinal fluid.
7 *Negative provocatives and positive* spinal fluid.
8. Early cardiovascular syphilis.
9 A negative spinal fluid, and positive neurological signs of syphilis, arrested tabes, gastric crises, Charcot joints, vascular syphilis of the brain.
10 Following positive serologic reaction and the reverse
11 Stigmata of congenital syphilis, including active interstitial keratitis.
12. Positive spinal fluid and negative neurological examination
13. Negative provocative negative spinal fluid and neurological examination, and positive eye signs of syphilis (peripheral chorioretinitis, congenital child with stigmata)
14 Negative spinal fluid, negative neurological examination, no stigmata of congenital syphilis, eighth nerve deafness, positive Bárány positive therapeutic test. (The infection in this case must be identified by examination of the family
15. A history of genital lesion, an eighth nerve deafness, anomalous genital signs, slight pleocytosis in the spinal fluid, paraesthesias and positive therapeutic test.
16. Negative clinical examination. Positive history and later positive findings on follow-up
17 Negative history and clinical examination. Returns later with positive cardiovascular signs.

Serological Tests and the Determination of Infectiousness.—The following statement, destined to be repeated in a subsequent chapter is placed here to catch the eye of the reader perusing this material merely for information on the serological tests. There are few misconceptions of which it is more difficult to disabuse the practitioner than the feeling that the serological tests for syphilis determine the infectiousness or noninfectiousness of a given case Once assured that his blood test is negative the patient takes it naïvely for granted that his liberty is restored and that he can once more from the standpoint of transmission of the disease *comport himself a a well man. Too often the* physician, acting under the same misconception encourages the patient in this delusion The facts of the matter are these **Infectiousness in syphilis is never determined nor is noninfectiousness proved by the outcome of any**

serological test, single or repeated. Noninfectiousness in syphilis is the result of lapse of time and absence of infectious lesions. While the serological tests tend to become negative with both time and treatment, and tend to be positive when infectious lesions are present, there is no necessary correspondence between the two. The exceptions to the rule are too often the most tragic that can be imagined. The wise physician will therefore allow no relaxation of any precautions he may have ordered against the transmission of the disease on the basis of the reversal of a blood test to negative or even of its persistence as negative over a considerable period. He will depend instead upon his knowledge of the age of the infection, the peculiarities of the individual case (for there is a definite infectious relapsing type), and on the results of prolonged systematic empirical treatment with the arsphenamines and the heavy

Fig. 40

THE CLINICAL CONTROL OF SEROLOGICAL TESTS

1. Accept no serological test as an infallible diagnosis or absolute exclusion, without clinical examination.
2. Accept no positive test without at least one repetition.
3. Know the conditions known or suspected to give biological false positives.
4. Insist that your laboratory run a complement fixation (Wassermann) and a precipitation test parallel on all specimens, and report both.
5. Insist on one semiquantitative report, especially in treatment and on spinal fluid.
6. Repeat all doubtful or indeterminate tests.
7. Repeat all negatives at least once if clinical suspicion warrants.
8. Avoid checking different laboratories against each other on the same specimen. Use only a laboratory which you know does this periodically en bloc. Individual practitioners' attempts at this sort of control rarely do more than confuse.
9. Laboratories working without clinical control, or refusing it, are apt to be inaccurate.
10. Serial repetition of a test with initial negative results with or without an arsphenamine injection (provocative) adds about 18 per cent to the possibility of obtaining an authentic positive.
11. A weekly test after treatment begins or is resumed, following a negative may during a month disclose a positive returning to negative (therapeutic provocative).
12. In seronegative primary syphilis one or two such tests are essential.
13. Provocative effects in the spinal fluid may be observed but are delayed.
14. Expect conflicting results in late syphilis; but question a laboratory which gets negatives or weak positives in acute secondary syphilis or untreated early paresis.
15. Distrust frequent reports of "clears slowly" and "anticomplementary" as reflecting on the laboratory as well as the specimen.

metals and on frequently repeated physical examinations with special reference to the regions in which infectious lesions are known to appear (see Chapter XIII). In particular he will never authorize the relaxation of precautions against the transmission of the disease in sexual intercourse merely on the strength of single or repeated negative serological tests.

The Two Types Used Simultaneously Are Essential.—The evidence for the ability of complement fixation to detect a proportion of undoubted positives not recognizable by precipitation and *vice versa* is too strong to be denied. Moreover, and this point, we believe, has been too easily overlooked by organizations which have given up complement fixation tests in favor of precipitation procedure, there is a vast body of knowledge accumulated around the positive and the negative Wassermann reaction which cannot be transferred except in the course of a rather long interpretative interlude, from the comple-

ment fixation to the precipitation test. This body of clinical knowledge is a priceless accumulation, the only code to which decision in the doubtful case can be referred. It may therefore be accepted as the sound opinion of the present day that no laboratory is performing its final duty toward the diagnosis of syphilis or serving its patrons properly which is not reporting the results of a complement fixation and a precipitation test simultaneously performed on every serum Screen tests are only preliminary

The Routine Blood Serological Test.—The first edition of this book was inclined to oppose the attempt to routinize serological tests for syphilis as part of every medical examination feeling the justice of the objection on the score of expense and dreading further substitution of a mechanical procedure for an alert, receptive highly suspicious frame of mind Inevitably however the trend is away from this first position Simplification is doing away with objections on the score of expense the perfection of the balance between specificity and sensitivity with striking increase in both, is giving to the modern serodiagnostic test a reliability much superior to the older Wassermann procedure. Whole fields of syphilis, particularly the osseous and the visceral, will inevitably be dependent to some extent on serological diagnosis for the initial clue if not the final confirmation. Wherever surgery touches syphilis to its notable discomfiture in the past, protection of patient from misdiagnosis and of surgeon from risk of infection, begins with the application of routine serological tests The disappearance of syphilis below the threshold of visibility under modern methods of treatment leaves large numbers of patients whose condition can be appraised or identified only by the habitual use of serological tests. The newer conception of the asymptomatic carrier discussed in the earlier chapters requires for evaluation and for the protection of individual and public health the absolute routinization of the blood test for syphilis. Mass serologic testing for the determination of the presence and prevalence of syphilis in population groups ("the Wassermann barbeque") has become established practice in public health and military medicine It is no longer justifiable to limit the recommendations for such testing to the age period of seventeen to twenty-five, for it becomes almost equally simple and inexpensive to apply to all medical examinations from the moment of conception to the hour of death But is the routine test sufficient? Not at all Inevitably it will become a crutch and not a clue the moment it is divorced from or substituted for the painstaking physical examination of the patient Just as all appraisal of the diagnostic worth of serological tests must end in the clinic as a court of last resort, so physical examination maintains the one and most essential check upon the blood diagnosis of the disease. It is precisely in the fields of cardiovascular and neurosyphilis, the most critical aspects of the syphilology of the future as it concerns the individual patient, that serological tests still have their highest margin of error

THE SPINAL FLUID EXAMINATION IN THE DIAGNOSIS OF SYPHILIS

The Clinical Importance of Spinal Fluid Examination.—Too often looked on merely *as a fad and the pet of specialists the spinal fluid examination has* fundamental importance in the detection of syphilis *per se* in the complete examination of the syphilitic patient once his infection is recognized by other means as an indispensable guide to treatment, and as a test for "cure" or arrest.

The earliest application of the spinal fluid examination to the detection of syphilitic involvement of the cerebrospinal axis was that of Ravaut, in 1903, and of Widal and Sicard which antedated the first performance of the Wassermann test on the fluid by Levaditi and Marie in 1906. One of the most important steps in the rapid popularization of the spinal fluid examination was the demonstration that syphilitic involvement of the nervous system occurred, not late in the disease but early and that the application of the spinal test in the primary secondary and latent period would often reveal st t of ffairs of great importance t the patient future, though not betrayed by any symptoms whatever By 1918 it as conclusively show that early neurosyphilis could be recognized by spinal fluid examination before the ppearance of secondary lesions.

Abnormalities of the spinal fluid often of the most pronounced type precede by months or even years the first signs that can be elicited by neurological examination, and the first appearance of symptoms of a subjective type. It has become apparent that there is no necessary correlation between symptoms and spinal fluid changes so that a person with every serological evidence of severe neurosyphilis may have no symptoms or other neurological findings, while one with severe symptoms may have a normal fluid The fact *that the spinal fluid in itself* may be the sole guide to an otherwise asymptomatic and obscure involvement of the most important group of structures affected by the disease, has justified the insistent demand of syphilologists that the test shall not be an optional part of the management of early and latent syphilis, but shall be an absolutely routine requirement for all ca es at the proper time during their course. As a guide to the effect of and need for treatment in both early and late neurosyphilis, the examination of the spinal fluid has become indispensable, and failure to insist on the test may rank as culpable negligence. Should the patient refuse it his blood is at least on his own head.

General Considerations.—The earlier in the course of a syphilitic infection the spinal fluid examination is done, the higher is the proportion of abnormal findings. Abnormal fluids are found in the primary stage in from 7 to 25 per cent of the cases. In the fully developed secondary stage untreated various reports range from 26 to 78 per cent, with a probable mean of about 40 to 45 per cent. In treated and more advanced untreated secondary syphilis, the proportion falls to from 24 to 20 per cent (A tabular summary of various reports up to 1936 is given by E. Lomholt, 1936) This may be regarded as the basic minimum of neurosyphilis which is not cleared up within the first two or three years of the disease either by the resistance of the patient or reasonably intensive treatment. It is from this group that the tabes and paresis, the vascular accidents and the multiple manifestations of cerebrospinal syphilis are in the later years recruited. It is for the existence of such a group that practitioner and patient who refuse to utilize spinal fluid diagnosis and modern therapeutic measures are responsible

The importance of the spinal fluid examination to the detection of neurosyphilis as an element in general medical and surgical diagnosis, likewise can hardly be overestimated.

An instructive study of this question was that of Stokes and Brown on the interpretation of the medical complaint of stomach trouble in the patient with syphilis. They found that the syphilitic patient with stomach trouble has lesion of the stomach or gastro-intestinal tract in only 10 per cent of 200 unselected cases On the other hand 75 per cent of syphilitic patients who complained of stomach trouble had neurosyphilis, and in 49 per cent of these it was detected or confirmed by spinal fluid examination, though only 44 per cent of the patients had positive blood Wassermann reactions, largely because of previous treatment. Only 10 per cent of the

entire series had had spinal fluid examinations as part of any previous examination, though 49 per cent were positive. Seventy per cent of the patients with persistently negative blood Wassermann reactions, not due to treatment, had positive findings in the spinal fluid.

It is important to note for reemphasis later that the spinal fluid does not invariably indicate the existence of a neurosyphilis, which none the less is present. This is notably the case in certain types of tabes dorsalis, including those presenting Charcot joints and gastric crises, and in the comparatively isolated involvements of vascular neurosyphilis and solitary gumma.

The Time to Do the Spinal Fluid Examination.—The enthusiasm of the clinician is usually when confronted with the exigencies of private practice obliged to make some compromise with circumstances. Theoretically the spinal fluid of the patient with early syphilis should be examined just after the third arsphenamine injection, provided there have been no indications for its earlier performance such as severe headaches meningismus, or symptoms from the cranial nerves. In practice, however the performance of the test at this time is a serious tax upon the relations of physician and patient and hence upon the continuity of the patient's treatment, upon which so much depends. So influential is reaction to lumbar puncture in defeating the aim of treatment as a public health measure that the entire venereal disease practice of Great Britain's Ministry of Health was conducted without reference to it, on the score of its discouraging effect upon the attendance of the worker at clinic. A compromise with the necessities in the individual case can usually be reached by adopting the following principles

1 Information on the state of the spinal fluid should be thought of as part of the preliminary or diagnostic work-up of all patients other than those with primary and secondary syphilis, who have positive blood serologic reactions on first examination. Without the information which it yields, treatment decisions are made in the dark. If puncture is refused and a groping approach is unavoidable one should proceed as if the fluid were abnormal.

2. In early syphilis under treatment, if the blood serologic reactions are still positive at the twenty-fourth week, the spinal fluid should be examined and in any event by the end of the first year before rest period or discharge to observation is granted.

3 In early syphilis treated by intensive foreshortened methods (one to fifteen-day or six to ten week systems) the spinal fluid should be examined before the completion of treatment or as soon as possible thereafter repeated within the year Leifer Chargin and Hyman (1941) examined their patients between the sixth and twelfth month

4 No resistant or fixed positive blood Wassermann or precipitation test can be interpreted or dealt with, without examination of the spinal fluid Such tests frequently mean concealed or asymptomatic neurosyphilis.

5 In persons under treatment in whom blood serologic tests have become repeatedly negative a relapse to positive should be followed by examination of the spinal fluid.

6 The spinal fluid examination must be repeated to determine the progress under treatment of any patient who has neurosyphilitic involvement. The frequency of repetition must be decided by indications in the individual case

7 *Pari passu*, the spinal fluid need not necessarily be examined

(*a*) Yearly or repeatedly as mere routine in patients who responding normally to effective treatment, have negative fluid findings with negative blood when treatment is completed and they are placed on observation Reasonable

clinical (relapsing type) or serologic indication should exist, for repetitions after the second post treatment year. This is especially applicable to early syphilis. In late syphilis, a negative fluid is almost never followed by a positive.

(b) When the spinal fluid findings cannot influence the course to be pursued in the individual case, e. g., a decompensated cardiovascular syphilitic involvement in which treatment is wholly governed by the cardiovascular status.

(c) In extreme old age regardless of the patient's status.

The Physiology of the Spinal Fluid.—The cerebral ventricles and the meningeal sacs covering the brain and cord contain from 100 to 128 cc. of limpid, waterlike fluid, secreted mainly by the choroid plexus but also receiving some additions from the perivascular channels communicating with the subarachnoid space on the surface of the brain (Howe). Kafka (Jadassohn Handbuch) cites Jacobi as having demonstrated some degree of secretion by the ependyma of the ventricles. While the larger part of the spinal fluid is therefore presumably the secretion product of the choroid plexus, and this structure, therefore, stands as a barrier between the spinal fluid and the blood, there is evidence to show that the condition of the spinal fluid reflects local processes in the meninges as well as the parenchyma of the nervous system and that its content may be modified by substances derived from the blood circulation. For example, Weed showed that in cats circulating meningococci could be carried over into the meninges by the effect of pressure reduction in lumbar puncture. *Spirochaeta pallida* has been repeatedly demonstrated in the spinal fluid with and without serological evidence of involvement. Sekiguchi and Kolmer showed that syphilitic reagin from Wassermann-positive human blood introduced into the vascular circulation of dogs, gave a slightly positive Wassermann reaction on the spinal fluid. The penetration of the spinal fluid by such drugs as iodine (Osborne) and arsphenamine has been repeatedly demonstrated. It has been shown in both Sekiguchi and Kolmer's work and Osborne's studies that secretion of drugs into the spinal canal is increased by a meningitis. It is evident, therefore, that under normal conditions the choroid plexus is the principal source and that only under pathologic conditions is it to be expected that the spinal fluid will contain considerable amounts of substances introduced into the circulation. The work of Weed and Carbett indicates that the injection of hypertonic salt solution into the blood stream dehydrates the nervous system and causes increased reabsorption of spinal fluid, while hypotonic solution causes an increase in the amount of spinal fluid. This observation has been utilized in certain forms of treatment of neurosyphilis. Withdrawal of large amounts of spinal fluid (spinal drainage) can be used as a method of draining the spinal canal and even the parenchyma of the nervous system of micro-organisms and toxic products. The method, for example, has been applied in treating toxic primary optic atrophies due to tryparsamide by repeated spinal drainage.

The spinal fluid secreted by the choroid plexus and other contributors has apparently been shown by Dandy and others to be absorbed through the meningeal vessels into the blood stream. Weed, however, has championed the view that absorption takes place through pacchionian granulations and arachnoid villi.

The rate of secretion of spinal fluid is probably very slow when the hydrostatic system is intact. If, however, puncture or rupture of the membranes occurs, secretion may be greatly accelerated and large quantities of fluid lost, through a very small opening. This consideration makes it extremely important to follow those technical details of lumbar and cisterna puncture which reduce the likelihood of leakage of the spinal fluid to the lowest possible terms. Greene, later confirmed by Shaffer's unpublished experiments, showed that the isolated lumbar sac lost very much less fluid through a puncture made with a conical as distinguished from a wedge or bevel-pointed needle, presumably because the fibers of the dura were separated instead of cut by the former point and spontaneous closure more readily took place. Pitkin has devised a needle point which he believes makes a flapped opening in the dura that closes on withdrawal of the needle. M. O. Nelson has shown that plugging of the opening with catgut reduces the incidence of lumbar puncture headache. These various contributory forms of evidence would seem to indicate that headache following lumbar puncture is the result of leakage and disturbed pressure equilibrium, as suggested by Marie and others. That nervous and other influences, however, affect the tension of the cerebrospinal fluid and may, therefore, contribute to reactions, is indicated by Solomon, Pfeffer and Thompson's observations of the effect of muscular tension and the nervous state of the patient in raising spinal fluid pressure at the time lumbar puncture is performed. Gennerich also has called attention to the relatively greater frequency of puncture reaction in high-strung neurotic patients.

From these considerations it will be apparent that the permeability of the choroid plexus and the meningeal capillaries is the critical point in attempting to introduce medication into the cerebrospinal canal by way of the general circulation. It would appear furthermore, that the amount of any given drug in the spinal fluid is a relative but not an absolute index of the permeability of the parenchyma of the nervous system as a whole. When it is desired to treat the meninges directly with a drug, the irritant effects of that preparation must be considered among the factors in treatment, and the possible "irrigating" effect of stimulating a more rapid secretion and absorption of spinal fluid must be taken into account, together with the effect of the introduced substance (as for instance blood serum in the Swift Ellis treatment) in inducing aseptic meningitis and freer absorption of arsphenamines and other medicaments introduced into the blood stream at the same time.

There exist certain differences in the cytology, composition and reactions of the spinal fluid at different levels, as, for example, in the ventricles and in the lumbar sac. These have been studied by Solomon and Ayer but they do not appear to have attained importance as a source of possible clinical error in diagnosis, except in cases of meningeal block, in which case it may be necessary to obtain specimens at different levels as part of the diagnostic study.

The Essential Tests and Findings—Gross Specimen.—The technic of obtaining spinal fluid for examination is considered on page 318 with a discussion of contraindications, complications and reactions. Adequate study of the spinal fluid after it is drawn is a matter for the laboratory. The operator, however, should observe (1) The color. (2) The pressure. (3) The physical state on withdrawal and after standing. Discoloration of a reddish or brownish tinge is produced by hemorrhage, recent or old. Even a very small trace of blood dims the limpid clearness of the fluid. A clear yellow fluid (xanthochromia) is suggestive of cord tumor. Simple turbidity or opalescence usually evidences a degree of meningitis rarely met with in neurosyphilis and is due to the large numbers of cells of the meningeal exudate. Increases in fluid pressure are observed and are of technical importance as a warning to withdraw fluid slowly and in small quantities, except in rare cases of brain tumor in which the probability of increased pressure should have been foreshadowed by neurological and ophthalmological examinations.

Precise pressure determinations have not, in our experience, been of enough importance to justify the practitioner or syphilis clinic in purchasing or using a manometer. Such equipment, however, is essential to the minutiae of neurological differentiation and for the purpose we recommend the portable jointed glass manometer for measuring the pressure directly, in preference to the mercury manometer (Ayer). Normal pressure readings range from 60 to 150 mm. of spinal fluid (Greenfield and Carmichael) and Baldunn has stated that dangerous complications do not arise if the cerebrospinal fluid pressure is not allowed to fall below 180 mm., even in a case in which excessive intracranial tension is present or feared.

Pressure measurements taken under ordinary condition or following painful punctures in nervous and frightened patients are untrustworthy. Marked reductions in the rate of flow are usually without diagnostic significance so far as syphilis is concerned, and indicate more often some obstruction of the opening of the needle or are dependent on the bore of the instrument.

Interpretation of Spinal Fluid Findings.—The spinal fluid as sent to the laboratory for test should be fresh, should be free from blood cells in gross or microscopical amounts unless such were present in it before its removal from the canal, should be sufficient in amount for all tests (8 to 10 cc.) and should be promptly examined. The same precautions in regard to container tubes and labeling should be used as with blood serological tests. Spinal fluid should not be exposed to sunlight (Silker 1941).

Mehrtens, Wyckoff and Davis have found that if blood is removed from spinal fluid by centrifuging, the type of colloidal curve remains the same but is altered in intensity. Loveman and Stocking (1934) found that blood contamination vitiates the Kahn test on the fluid, and Solomon et al. (1934) were able to reconstruct all findings in blood containing specimens, except the serologic test in patients who were also positive on the blood. In patients with general paralysis whose spinal fluid has become negative through treatment, contamination with blood produces a tendency to revert to the original curve. The original colloidal gold curve of spinal fluids experimentally contaminated with the patient's blood can be approximately reconstructed provided hemolysis has not occurred. Colloidal tests in particular are affected by hydrogen ion concentration to some extent, and cell counts to some slight extent, by standing.

Blood in the spinal fluid as a result of puncture, suggests inexperience or technical error. It is advisable however even in a perfect entry to allow at least 30 drops of spinal fluid to flow from the needle before the collection of the fluid into the first of the three test tubes is begun. The cell count should be made by the laboratory from the third tube.

Essential Laboratory Tests.—Upon the spinal fluid four absolutely essential tests should be performed for purposes of syphilological diagnosis, as follows:

1. A quantitative Wassermann test, on more than one quantity of fluid (0.2 and 1 cc.) is generally accepted as preferable to the precipitation tests on spinal fluid which are still in the investigative stage. The Reiter spirochetal antigen is reported to be highly specific in spinal fluid serology. The quantitative Kolmer test is in our experience the most satisfactory.

2. A globulin estimation which may be either a Pandy, Noguchi or Nonne for ordinary purposes, but which will probably be ultimately some form of total protein determination.

3. A cell count, which distinguishes lymphocytes and polymorphonuclears if present and identifies red blood cells.

4. A colloidal test, upon which much of the differential prognosis depends. For this purpose the gum tests with benzoin or mastic are preferable to the usual colloidal gold tests, which are well performed by very few laboratories.

Eagle (text 1937) and Moore (treatment, 1941) in recent writings tend to minimize the clinical importance of colloidal tests in the differentiation of types of neurosyphilis, and to suggest the possible substitution of total protein and globulin-albumen estimations as simpler and more trustworthy. With O'Leary' (1944) objections to this proposed simplification we are essentially in accord. The technic of estimating albumin-globulin ratios and total protein content of the spinal fluid still contains many elements of uncertainty to be ironed out, as can easily be recognized in the surprising reports received from otherwise competent laboratories even on apparently normal fluid specimens. The colloidal tests have, moreover, become a dependable part of the international language of syphilologists, and about them a large body of clinically usable and effective knowledge has been built up. The translation of that knowledge into terms of protein estimation will require many years of combined clinical and laboratory study such as is not yet even completed for the more easily studied complement fixation and precipitation tests for syphilis on the blood serum. It would seem wiser therefore if for no other reason than that of universality of usage and reasonably demonstrated dependability with a known margin of error to continue the use of the simpler colloidal tests, such as the mastic, indefinitely pending the evaluation of protein-globulin relationships in this as well as other fields of medicine.

A quantitative test for sugar (Folin and Wu, Hagedorn and Jensen, Greenfield and Carmichael) need not be done as a routine but is used in differentiation in neurological cases (encephalitis) and should be requested if desired. An increased amount of fluid is required by some methods. The normal ranges between 45 and 85 mg. per 100 cc., usually 48 to 63 mg. according to various authors.

The willingness of physicians to accept or to think in terms of spinal fluid reports containing information only on the Wassermann test, and the practice

of smaller laboratories in reporting on this basis, cannot be too strongly deprecated. All four tests are essential and act as crosschecks on each other. The quantity of fluid routinely obtained should be sufficient for all four tests (8 to 10 cc.) and reports should be rendered on all. No complications in the writer's experience are induced by the obtaining of a sufficient amount of fluid provided the patient is one who should have been punctured for diagnosis at all and provided the fluid is allowed to drip very slowly.

The Spinal Fluid Cell Count.—In the course of neurosyphilitic involvement, especially in the earlier or asymptomatic years, the successive elements in an abnormal picture tend to appear in a more or less constant succession which will be used in describing their significance. A rise in cell count or a slight increase in globulin is the simplest form of reaction observed and the rise in globulin, even more than the cell count, is the most persistent abnormality under treatment, though it is at the same time the most responsive to treatment so far as reduction in the number of cells or amount of globulin is concerned. The cell count differs from the other three standard tests of the fluid in that it must be performed within a short time after the fluid is obtained for accurate results. It is, moreover, vitiated by the presence of any appreciable amount of blood contamination of the fluid even though a means of laking the blood cells be used.

Loren Shaffer carried out a brief but instructive series of unpublished studies on the relation of the cell count of the spinal fluid to the time after withdrawal at which the count was made. He found that the chief error came through sedimentation of the cells on standing. The tube and its contents must be strongly shaken to form a uniform suspension before counting. Great variations may occur through withdrawing fluid from various depths in the test tube, very low counts being obtained from the upper layers and very high counts returned when the fluid is taken from the bottom of the tube. Furthermore, the cells have a tendency to adhere firmly to the walls of the test tube when the fluid has stood for some time. The suspension being uniform, however, cytolytic deterioration seemed to occur at an almost uniform rate of about 20 per cent in each twenty-four hours.

Cell counts on the spinal fluid should in general be made with one of the newer counting chambers such as the Fuchs-Rosenthal. The leukocytes in the fluids are differentiated by staining with Unna polychrome methylene-blue solution which is drawn into the ordinary white blood cell pipet to the first mark (1). The remainder of the pipet is then filled with spinal fluid. Before drawing into the pipet the fluid should be thoroughly shaken in the test tube to assure an even distribution of cells. The count may be made within two or three minutes after the stain is added. All the cells in the entire ruled area of this chamber are counted, the slight dilution with stain being disregarded, and the total divided by 3 for the actual count. If the fluid contains a large number of cells or if a Türk or Thoma-Zeiss chamber is used, the dilutions and count should be made as for a leukocyte count on blood. The addition of acetic acid to the staining mixture is not necessary if polychrome methylene-blue is used, and this stain has the added advantage of affording some differential staining of plasma cells without staining the red blood cells. Moore counts all cells in the field with undiluted fluid and multiplies by 10/9 for accuracy.

The cell count of the spinal fluid is an index of meningeal reaction, that is, of leptomeningitis. It is, therefore, an entirely nonspecific finding and no diagnosis of syphilis of the nervous system can ever be based exclusively upon a rise in the cell count of the spinal fluid. None the less, in conjunction with other clinical and serological evidence, even a very slight rise in cells may be quite significant. Inasmuch as meningeal reaction is one of the earliest forms of pathologic change in many neurosyphilitic processes, the cell count assumes great importance as a warning of trouble, actual or impending.

The typical cell of the spinal fluid in neurosyphilis is the small lymphocyte as distinguished from the polymorphonuclear leukocyte of other forms of meningitis and early poliomyelitis.

Too much emphasis should not be laid on this point. Large lymphocytes may be present to the extent of 80 per cent and in high cell counts polymorphonuclears may reach 3 to 30 per cent, the latter in intraspinally treated patients or after repeated puncture without serious significance. Plasma cells appear at times in the fluid of paresis but are not diagnostic. Squamous endothelium from the subarachnoid space may be disregarded.

The absolutely normal count ranges from 1 to 3 lymphocytes per cu. mm., but an upper limit of 4 cells may be regarded as within the range of normal. Nonne places the upper limit at 5 cells, Greenfield and Carmichael at 3 cells, the presence of 4 cells per cu. mm. in a good specimen being suspicious. So far as syphilis is concerned, cell counts of from 5 to 10 lymphocytes per cu. mm. are the very definite beginnings of the abnormal, and cell counts above 10 are absolutely abnormal. In the examination of the spinal fluid of persons known to have syphilis and to be either within the first two or three months of the disease or under the influence of treatment, slight increases in cell count are distinctly significant. Thus a patient with early secondaries who, following his first 2 or 3 arsphenamine injections, has a cell count ranging from 6 to 10, is showing distinctly suspicious evidence of meningeal reaction. Such a count demands a reexamination of the spinal fluid before he is placed on any form of rest interval. Counts of this type are also obtained in the first spinal fluid examination of a treated patient with early syphilis when this is examined from twelve to eighteen months after the onset of the infection. Under these circumstances they cannot be regarded as normal and warn of the possibility that as soon as a rest period is allowed the patient may suffer some form of neurosyphilitic relapse.

The very definitely abnormal cell counts in neurosyphilis range from 10 to 1500 cells per cu. mm. and even higher. In the special type of syphilitic leptomeningitis associated with prenatal syphilis, the cell counts may be so high as to resemble those of a purulent meningitis and the large number of cells may produce an actual turbidity of the spinal fluid. High cell counts (up to 1000) also occur occasionally in the basilar meningitis of early syphilis and neurorelapse. Very low cell counts may be associated with grave processes, and counts of 2 to 7 cells with strongly and persistently positive Wassermann reactions on the fluid. The independence of the meningeal phase of neurosyphilis and its greater responsiveness to treatment are illustrated by the observed return of cell counts to normal without notable improvement in either other fluid or blood findings, or of symptoms. The average range of cell counts in active neurosyphilis is from 12 to 100, the larger number of the cases falling in the range between 24 and 50. Ravaut and Boulin, cited by Eagle, believe the lymphocyte and small mononuclear cell are representative of mild meningeal reaction, large mononuclear and plasma cells appearing in the more serious parenchymatous involvements including paresis.

The height of the cell count has a certain prognostic significance, and it is possible to show quite definitely that a spinal fluid with a strongly positive Wassermann reaction and a low cell count has a less favorable prognosis than a similar fluid with a high cell count. The cell count is subject to variation after treatment in the form of increases in the count—coming on the second, third and fourth weeks after treatment is initiated and having therefore presumably the character of a Herxheimer reaction or therapeutic flare-up. Quite marked ups and downs in count may occur in serial punctures or be induced by treatment with or without so-called "spinal drainage" ("seesaw counts"). Illustrations of these types appear in Chapter XX.

The Globulin Estimation on the Spinal Fluid.—The increase in the protein of the spinal fluid in pathologic processes is presumably another phase of the meningitis and as such is entirely nonspecific in character It is therefore impossible to prove the existence of a syphilis of the nervous system by an increase in globulin *per se* The globulin estimation has only a limited diagnostic significance but increasing emphasis is being placed on its prognostic value. A total protein estimation thus becomes a very helpful guide to the progress of a treated neurosyphilitic case

A good many objections may be offered to globulin tests as guides to spinal fluid abnormality Those in common use are qualitative rather than quantitative, do not give clue to the albumin-globulin ratio, and of course give no total protein estimation. None the less, their comparative convenience makes such procedures as the Nonne ammonium sulphat precipitation, the Pandy phenol test and the Noguchi butyric acid test still popular for ordinary laboratory purposes. They are usually returned in reports as negative 1 plus or 2 plus, and more exact readings can be obtained by centrifuging graduated capillary tubes (Jadassohn Handbuch) Lange (1930) reviews the precipitation methods. Nephelometric equipment is expensive, requires experienced handling and gives only qualified results. The normal reading according t various authors ranges (Hinrichsen, 1941) from 25 to 75 mg. per cent. The micro-Kjeldahl method remains the standard of reference. A colorimeter method using sulfosalicylic acid is being increasingly used.

The Colloidal Test on the Spinal Fluid.—It is a little difficult for the clinician to realize that the colloidal test, like the cell count and the globulin estimation, is quite largely nonspecific in character and that it is impossible absolutely to confirm or negate a diagnosis of yphilis by this test alone. None the less, the colloidal tests furnish better evidence of the existence and character of a syphilitic involvement of the nervous system than any other of the tests except the Wassermann In the performance of these tests, whether by the use of colloidal gold, colloidal benzoin or colloidal mastic, a series of tubes, 10 in number in the gold and mastic tests and 15 in number in the benzoin test, contain the colloidal suspension, and a series of color or turbidity changes are induced which are expressed by a series of numerals. Thus, an absolutely normal colloidal test with the gold or mastic technic is read as a series of 10 zeros, 0000000000 A negative colloidal benzoin test, on the other hand may read as a series of 15 zeros or there may be a change in the middle portion of the series so that it reads as follows 000 000 033,310 000 A certain amount of variation from the absolutely zero and negative curve is allowable and a mastic of 1100000000 is regarded as negative. This is, in a sense, a nonspecific margin. A gold or mastic test of 0112100000 must be regarded as indeterminate (no reading over 2)

The colloidal gold or gold sol test, discovered by Lange in 1912, was the outcome of Zsigmondi' studies of the ction of albumins on colloidal gold suspension. It is purely an empiric test, apparently expressive of the concentration and physical state of the globulin in the spinal fluid. The work of the English investigators, Wright and Kermack, and also of Shaffer would show that the hydrogen ion concentration plays highly important part in determining the types of precipitation produced by spinal fluid in colloidal benzoin or colloidal gold solution. There are seemingly two substances in spinal fluid causing precipitation of colloidal solution. The substance causing precipitation in zones 2 and 3 acts at lower pH value than that which causes precipitation in zone 1. The factors determining these zones are fixed by the technic of the tests and are dependent on the alkalinity of the spinal fluid, the pH of the colloidal solution and the grade of dilutions of the spinal fluid. While this work gives physicochemical explanation of the precipitation, the true nature of the precipitating substances is as yet undetermined, except that they seem to be contained in the globulin or pseudoglobulin fractions of the spinal fluid. The colloidal benzoin test, introduced by Guillain, Laroche and Lechelle, with modifica-

tion advised by Wright and Kermack in the preparation of the alcoholic extract of gum benzoin, is a very satisfactory test, requiring slightly more spinal fluid than the gold or mastic. The mastic test, devised by Emanuel in 1915 and described by Cutting, is a relatively simple and trustworthy test which is used routinely in the laboratory of the Johns Hopkins Syphilis Clinic and in our own laboratory.

We personally feel that under ordinary conditions of performance mastic or benzoin should replace colloidal gold, for the gold reagent is relatively difficult to prepare and only in the hands of occasional laboratory experts or very experienced technicians gives constant and reliable results. The mastic test has a tendency to read slightly toward the paretic side but with a little experience this can be interpreted and one escapes entirely the repeated fluctuations and "humpy" and uninterpretable results too often returned by the gold test.

The Paretic and Luetic "Zones."—The two types of the positive colloidal test which are of importance in the interpretation of neurosyphilis are the so-called "first" and "second zone" or "paretic" and "luetic" curves. The so-called "paretic or first-zone curve" as represented in the numerical form always reads high to the left. In other words, in the colloidal gold test a typical paretic curve would be 5555432100. In the benzoin test it reads 333,333,332,100,330. In the mastic test the readings in the first-zone curve may range from 3333321000 to 5555531000. The first zone test is the best defined and most distinctive in all three procedures. The second zone test is apt to be indeterminate with the benzoin and mastic methods. Colloidal tests are capable of expressing a certain degree of intensity of reaction so that a paretic first zone test may read 2222100000, a curve of much less intensity than one of 5555432100. Such changes may occur under treatment and they are also well known to constitute fortuitous variations in successive readings under varying physiologic and laboratory conditions. The luetic or syphilitic curve, an accompaniment of other forms of neurosyphilis than paresis, reads in all three types of test, "high in the middle and low at both ends." Thus, a typically intense gold sol test would read 0124554100. Milder types of this curve would not reach 5 on the middle tubes.

Other Types of Curves.—Various atypical curves are observed from time to time in the examination of the spinal fluid of all patients, whether they have syphilis or not, and these variations can only be discounted by experience. Atypical curves may have one or two high digits at the left with marked irregularities throughout the remainder of the series. Tests with no reading above 2 and sometimes even frankly negative tests must be regarded, in accordance with the circumstances of the case, as indeterminate in character and subject to special interpretation.

A third type of curve occasionally seen with gold sol and benzoin in patients who have coincident syphilis with other diseases of the nervous system is high on the right, the so-called "meningitic curve" (0001233345) which is without significance as regards the diagnosis of neurosyphilis, except in a negative way. Its occurrence with slight increases of cell count and protein with negative Wassermann on fluid and blood suggests so-called "multiple sclerosis."

It is extremely important to emphasize, in dealing with the colloidal tests, that, like all serological procedures, they are subject to error and that a single test which conflicts with the clinical facts must not therefore be accepted as gospel. Rayner in 2100 spinal fluids obtained best agreement between gold and mastic tests (91 per cent) with mastic and benzoin agreeing in 81 per cent. He rates the benzoin as the most sensitive procedure. In labeling a certain type, such as zone 1 as "paretic," emphasis must be placed on the fact that

while a paretic curve is invariably of serious prognostic significance, it does not by any means invariably mean that the patient is destined for a paretic outcome In fact, the interpretation of a paretic curve is sometimes, especially in early syphilis, impossible at the outset and must depend on the repetition of the finding, on its response to treatment and most especially on its relation to other items in the four serological tests on the fluid and the serological tests on the blood in both the original and subsequent examinations Notwithstanding this necessity for cautious interpretation the first zone colloidal test in its presence or absence is the one most important single prognostic item in the spinal fluid examination with respect to syphilis.

The Spinal Fluid Wassermann and Precipitation Tests.—The spinal fluid Wassermann test is the most specific test in the entire series and the only one which points, when definitely positive directly to the diagnosis of syphilis. It should invariably as has been said be performed by some type of quantitative procedure, of which we personally can commend the Kolmer It is essential to do a quantitative test because in the spinal fluid the Wassermann reaction may not appear positive until the larger amounts of fluid are employed. This is especially true very early in the disease when the meningeal reaction is the chief pathologic phenomenon and likewise quite late in the disease when the entire neurosyphilitic process is dying out. No physician therefore should ever be content to receive from the laboratory the simple statement that the Wassermann reaction on the spinal fluid is positive or negative. It is essential in interpreting the prognostic significance that he know on how much fluid within the range of 0.2 to 1 cc. the Wassermann reaction is positive. The quantity of fluid used is five to ten times that of the serum in the blood Wassermann test, which greatly increases its value in the detection of syphilis. The fluid is anticomplementary only when contaminated with bacteria (Harrison)

While in all probability precipitation procedure on the spinal fluid will ultimately challenge, if it does not displace, the Wassermann procedure it cannot be said that a sufficient body of information has accumulated as yet to permit the substitution of one for the other at this time, or even to recommend that, except for study purposes, both tests be performed in the routine laboratory

The Positive Spinal Fluid Wassermann Test.—Considerable variation in the degree of positiveness of the Wassermann reaction on the spinal fluid in various types of neurosyphilis occurs. A fluid may be Wassermann negative throughout in an active progressing neurosyphilis In early neurosyphilis associated with the primary and early secondary systemic lesions in which the pathologic changes are almost entirely meningeal and vascular the Wassermann test is negative at the outset, and in the small amounts of fluid even later It may only begin to be positive in amounts as high as 0 8 and 1 cc or in the first tube or two of the Kolmer test (40000) On the other hand strong positives may occasionally be obtained throughout all concentrations in very early cases. In late neurosyphilis of the tabetic type, while the test may be negative on 0 2 cc., it seldom fails to be partially positive on 0 4 or 0.5 cc., and is usually strongly positive on 1 cc The literature shows 54 per cent positive fluids in tabes (Browning and Mackenzie) In diffuse neurosyphilis ("cerebrospinal" syphilis) the proportion of strong positives in the smaller amounts of fluid is high (80 per cent, Browning and Mackenzie) In typical paretic neurosyphilis it is almost a reflection on the sensitiveness of the test

if it is not strongly positive throughout all concentrations. In cases confirmed by autopsy Mott found 98 per cent positive in 1910 Browning and Mackenzie 91 per cent in clinical paresis, in 1921 In preponderantly or purely vascular syphilis, on the other hand the Wassermann reaction on the fluid is frequently negative in all concentrations, and persistently so. In general it has been our experience that strongly positive Wassermann reactions on all concentrations of the fluid persisting through repeated examinations of the fluid and in spite of vigorous treatment have a peculiar gravity and seem to be associated with those parenchymatous involvements that express themselves clinically as general paresis. It is this trend of observation in our own experience which leads us, perhaps without adequate anatomical justification, to interpret the positive Wassermann reaction in the spinal fluid in untreated cases as a rough index of the grade of parenchymatous change and to consider that complete and persistent negativity with convincing evidence of an active neurosyphilis suggests vascular involvement. Such differentiations should not be carried too far The types of active neurosyphilis now known to be associated with a practically normal spinal fluid to be alluded to presently must, of course be included in the group in which the Wassermann test is no guide to the presence or absence of specific involvement.

The False Positive Spinal Fluid Wassermann Test.—In spite of the superior accuracy of the spinal fluid Wassermann procedure, undoubted false positives, both technical and biological do occur Kolmer endorses Boerner and Lukens's discovery of the use of egg albumen (1941) added to the fluid to prevent false positives in his test.

The technical false positive is perhaps the easier to recognize because of the cross check afforded by the other three tests performed on the fluid. A fluid absolutely normal to protein, colloidal test and cell count, with a strongly positive Wassermann reaction on one or all concentrations, is almost undoubtedly a technical false positive and should be repeated and rechecked against clinical findings before anything decisive is done. Biological false positives were reported by Zadek in 1918 in 5 cases of meningitis and in 1927 Zange summarized the literature since Zadek's report. Schaffle and Riesenberg (1928) added to the possible sources of error tuberculous and other forms of meningitis, especially purulent meningitis following otitis media. Cerebral neoplasms and medullary tumor cases have been reported by Simpson and Loewenberg. Malcolm reports 8 atypical Wassermann reactions in 846 spinal fluids, of which only 1 however, was positive with the Kolmer test (cerebral tumor) In this series were cases of bulbar paralysis, encephalitis lethargica, anterior poliomyelitis and tuberculous meningitis. Schaffle and Riesenberg's cases included 8 nonsyphilitic cases, 4 with pulmonary tuberculosis, 6 of the fluids containing tubercle bacilli and 1 a traumatic meningitis with intracellular diplococci. McLean and Munger (1936) reported false positives in encephalomalacia, streptococcus septicemia, electrical burn, extrathecal pneumonitis, various injuries, multiple sclerosis. Kuske (1936) found no positives in latent syphilis and gonorrhea treated with malaria. It appears that the presence of micro-organisms predisposes to a false result. True nonspecific positives were seen in 2 cases of influenzal encephalitis. The presence of small amounts of seropositive blood may produce positives.

Interpretation of the Four Tests.—Nothing is more important than for the clinician using the spinal fluid findings in the study of syphilis whether in diagnosis, prognosis, or treatment, to realize that it is the ensemble which the tests performed on the fluid present, plus the blood serological findings and results of the physical and neurological examination and not the individual elements, which make the diagnostic picture and decide the issue Objections raised against the specificity of the four tests individually thus lose their force if clinical experience shows that certain combinations of them are presumptive evidence of one or another state of affairs in the nervous

system It is the importance of interrelation and cross interpretation of all the four tests in terms of each other which makes spinal fluid examinations of comparatively little value that do not include a cell count, or which consist of a Wassermann test on one concentration only which omit the colloidal reaction or are unaccompanied by blood serological neurological and if possible ophthalmological findings.* Worthless spinal fluid reports, covering a battery of tests impressive on paper but so internally conflicting as to be obviously erroneous and uninterpretable are still a distressingly frequent source of consultant s headache

Rating the four fluid findings in order of their general significance we would place the Wassermann reaction first the cell count next, the properly performed colloidal test third and the globulin estimation last in order of importance in reaching a conclusion as to the status of a neurosyphilitic infection No one of these elements, not even the Wassermann reaction can stand alone without question.

Interpretation of the So-called "Normal" or "Negative" Spinal Fluid.—The normal spinal fluid typically reads as follows Wassermann reaction negative on 0.2 and 1 cc or Kolmer Wassermann, 0000 globulin present in normal amount cell count, 3 colloidal test (gold or mastic) 0000000000 The normal spinal fluid while an important index of the absence of neurosyphilis, can never be accepted as absolute evidence that the nervous system is not involved by the disease Both active as well as arrested neurosyphilis may present completely and persistently negative spinal fluid to all four tests This, as Solomon has pointed out, and our own experience confirms, is particularly true of vascular neurosyphilis, of those forms of tabes dorsalis associated with gastric crises, Charcot joints and trophic ulcers, of cerebral nerve palsies, cerebral gumma, syphilitic epilepsy Erb s syphilitic spastic paraplegia and nonparetic syphilitic psychoses As previously stated it is even possible for the spinal fluid to contain the *Spirochaeta pallida* and yet be entirely negative to all four tests It may be said, however in spite of these qualifying remarks, that the negative spinal fluid is better presumptive evidence of the absence of syphilis in the neurological field than is the negative blood Wassermann reaction in general medicine It may moreover be said that a negative spinal fluid even in the presence of a neurological condition, almost excludes general paresis from the diagnosis. The question of the existence of seronegative paresis is as yet undecided, but there are some indications that general paresis in a preponderantly vascular phase may be almost if not quite seronegative in the spinal fluid, at least after treatment, and yet still be active and symptomatically progressive. Cases of this sort, however are so rare that they need hardly enter into the diagnostic rules applicable to ordinary practice

Interpretation of the Positive or Abnormal Spinal Fluid.—Emphasis has already been placed upon the significance of slight grades of meningeal reaction in spinal fluids obtained early in the course of a syphilitic infection whether in treated or untreated patients. An even greater emphasis in the interpretation of spinal fluid serology should be placed upon what we now label "the red flag."

This combination of the strongly positive spinal fluid Wassermann with a moderate or marked increase in cell count, a sharp but not excessive rise in globulin and a first zone colloidal test, especially when it occurs in conjunction

* These interrelations are more fully discussed in the various sections on early and late neurosyphilis

with a strongly positive blood serological test is, like the rattle of the rattle snake a warning of something serious to come This type of fluid is, of course the earmark of parenchymatous neurosyphilis of the paretic type and it like wise accompanies the so-called "neurorecurrence or acute flare-up of neurosyphilis that develops following suspension of treatment when an abnormal spinal fluid has not been recognized by previous examinations. It is impossible to overemphasize to the physician the seriousness of this spinal fluid picture

Fig 47

THE "RED FLAG OF PARESIS

CSF WR ///// 0.2 cc Nonne positive. Lymphocytes 70 Gold Sol 5555553321
/// 0.4 Colloidal benzoin 555,555,555,555,210.
/// 1 0

Fluids of this type resembling the preceding, but in which the first-zone gold sol reaction is of great intensity are almost invariably paretic, though the fluid picture must be interpreted in terms of the neurological picture Early clinical signs re pt to be present.

NO TIME FOR "NEO" NOW TRYPARSAMIDE? FEVER?

It is an immediate and unescapable warning that only the most effective and intensive of modern methods of treatment will be of any avail in checking the process going on in the nervous system Patients who up to this point have been treated by less intensive methods must, upon the appearance of this "red flag," be considered as candidates for tryparsamide and fever therapy unless they make an immediate response to a great increase in the intensity of standard treatment measures Whenever such a spinal fluid appears

Fig. 48.

THIS IS THE FLUID OF ACUTE SYPHILITIC MENINGITIS AND NEURORECURRENCE

CSF Kolmer WR 44441
WR /// 0 2 cc. Nonne positive. Lymphocytes 207 Gold Sol 5554451100.
/// 0.4 Colloidal benzoin 022,200,002,200,000.
/// 1.0

This is the fluid of acute meningovasculoparenchymatous early neurosyphilis with the meningeal phase especially prominent. It is not uncommon in the so-called "neurorecurrence" after inadequate treatment. Such cases may show symptoms of basilar meningitis—headache, dizziness, palsies, etc., but do not necessarily do so. It is this type of fluid in particular which calls for intensive treatment if the process is not to go on to an unfavorable outcome. The response is usually good. In late syphilis this type of spinal fluid may be associated with rapidly progressive cerebrospinal involvement or general paresis.

TREATMENT MUST BE INTENSIFIED "RED FLAG"

repeated examinations, the first repetition within an interval of three months at the utmost after the first test, are absolutely essential as treatment controls Once the physician in ordinary practice learns to seek for and properly interpret this 'red flag" or warning picture in the spinal fluid, grave neurosyphilis, and general paresis in particular can be greatly reduced in frequency

A Convenient Desk Card.— Recent American writers on neurosyphilis including the Cooperative Clinical Group, have employed in their discussions

the prognostic grading or typing of spinal fluid originally suggested by Moore and Hopkins (1933) This condensation gives in highly practical form the characteristics of three grades of spinal fluid abnormality observed in various

Fig 49

THE MENINGEAL REACTION IN EARLY SYPHILIS
(USUALLY ASYMPTOMATIC)

CSF Kolmer WR 45100
WR negative 0.2 cc. Nonne positive. Lymphocytes 101. Gold Sol 0155490000
0 4
1.0

In this patient the meningeal phase is uppermost and the outlook for a favorable response is good. Such fluids are common in early syphilis. It is possible that a marked vascular element will be found to underlie this picture, and fluid of this type during latency is essentially that of a meningovascular syphilis. Gummatous pachymeningitis of the cortex may present similar picture, but with much less meningeal reaction.

NEVER UNDERRATE EVEN A SLIGHT RISE IN CELL COUNT

aspects of syphilis with the prognosis and general treatment indications for each (Fig. 50) For one called upon to make decisions, this classification has exceptional practical value. Such a table however should not cause one to

Fig. 50.

PROGNOSTIC TYPING OF SPINAL FLUIDS
(Adapted from Moore and Hopkins 1933 and O'Leary et al. Reprint 62 Ven. Dis. Inf. 1937)

Type	I (Mild).	II (Moderate)	III (Severe)
Blood Serologic Reaction	Negative or positive	Negative or positive.	Almost invariably strongly positive.
CSF Quantitative Wassermann	Negative 0 2 cc. to 1.0 cc.	Negative 0.2 cc.; positive 1 0 cc	Strongly positive 0 2 cc. to 1.0 cc.
Cells	5 to 25	25 to 100	7 to 100 plus†
Protein	1 plus	2 plus	3 plus
Colloidal Test	1110000000 0000011000	00244543100	5555543100
Prognosis	Clears with standard or routine treatment for the disease	Requires 1 to 2 years additional standard plus intraspinal or fever	Will not clear without fever or tryparsamide, or both.

*Colloidal mastic or gold, preferably the former
†10–20 large lymphocytes and polymorphonuclears may be present.

lose sight of the fact, repeatedly emphasized that neurosyphilis can exist and progress in the presence of a completely normal spinal fluid and negative serologic tests on the blood

A spinal fluid report which always seems to be interpreted with great difficulty is shown in Fig 52. Granted that the blood Wassermann reaction in this case is negative thus is the fluid of so-called multiple sclerosis and is not at all diagnostic of neurosyphilis, in spite of the first zone colloidal test. A mere slight rise in cell count (7 to 15 cells) with a slight increase in globulin and negative Wassermann and colloidal tests occurs as an accompaniment of a good many systemic infections, as Herrick and Dannenberg have shown

Fig 51

LATENT NEUROSYPHILIS, OFTEN ASYMPTOMATIC

CSF Kolmer WR 44451
WR /// 0 2 cc. Nonne positive. Lymphocytes 47 Gold Sol 5455544100
/// 0.4 or 0125443210.
/// 1 0

This is not uncommon spinal fluid picture absolutely asymptomatic, serologically negative latent syphilis. There is moderate grade of meningeal reaction. The gold sol suggests the possibility of fa orable response to treatment.

THE REASON FOR ROUTINE SPINAL FLUID EXAMINATION

and must be interpreted in conjunction with the case. Occasionally there seems to be a tendency for partially or weakly positive Wassermann reactions to appear in the spinal fluid of patients with lethargic encephalitis, a fact which is sometimes the source of a good deal of difficulty in differentiation from general paresis. Anticomplementary Kolmer reactions on the spinal fluid and so-called "humpy Kolmer tests (04021) are sometimes quite difficult of interpretation but usually should be regarded as positive.

Fig. 52.

THE FLUID OF MULTIPLE SCLEROSIS, NOT PARESIS

CSF WR negative 0.2 cc. Nonne positive. Lymphocytes 17 Gold Sol 5555555210.
0.4
1.0

This fluid is seldom syphilitic. It is much more suggestive of multiple sclerosis. It must be said, however that t times defective batch of gold solution will yield crops of first-zone curves that cannot be trusted. With luetic curve (0134431100) this fluid ould be entirely compatible th a diagnosis of early meningovascular lues in the primary or secondary stage, provided it is supported by other findings. It would also accord with diagnosis of either early tabes, or lat degenerative type of tabes, often associated with gastric crises.

MULTIPLE SCLEROSIS MAY DECEIVE BY NONSPECIFIC TREATMENT RESPONSE

It cannot be overemphasized that the spinal fluid examination can never yield its best diagnostic possibilities when interpreted alone. It is part of the general medical and neurological examination of every patient who has syph ilis, and only in conjunction with findings on examination and the coincident serological tests on the blood can its real significance be evaluated. It is proper too, to reemphasize the fact that the blood may be serologically negative and the spinal fluid present definite evidence of neurosyphilis. Accordingly a spinal fluid examination supplies part of the necessary information for the

Fig. 53.

RELATIONSHIP OF BLOOD WASSERMANN REACTION AT TIME OF LUMBAR PUNCTURE TO CEREBROSPINAL FLUID ABNORMALITIES IN VARIOUS PHASES OF SYPHILIS (COOPERATIVE CLINICAL GROUP STUDIES)

Type of Syphilis	Spinal Fluid Positive Blood Positive		Spinal Fluid Positive Blood Negative.		Spinal Fluid Negative Blood Negative		Spinal Fluid Negative Blood Positive.		Remarks.
	Number	Per cent.	Number	Per cent.	Number	Per cent.	Number	Per cent.	
EARLY SYPHILIS—2117 Cases.									
(Excludes cases with clinical neurosyphilis)	404	19.1	178	8.3	743	35.1	748	35.3	46 cases no data 2.2 per cent (31 negative, 15 positive spinal fluid).

ASYMPTOMATIC NEUROSYPHILIS—458 Cases.

Type of Syphilis	Number	Per cent.	Number	Per cent.	Total. Number	Total. Per cent.
Early syphilis	130	69.1	58	30.9	188	100.0
Late syphilis	209	77.4	61	22.6	270	100.0
Early and lat syphilis Total cases.	339	74.0	119	26.0	458	100.0

All cases were treated prior t spinal test.

Fig. 43.—Continued.

SYMPTOMATIC NEUROSYPHILIS—1303 Cases.

A Arsenical Treatment Preceding Tests—625 Cases.

									Total Number	Total Per cent.
Tabes	370	80.7	114	31.2	24	3.2	18	3.9	462	100.0
Paresis	114	91.2	11	8.8					125	100.0
Taboparesis	57	85.1	10	14.9					67	100.0
Meningeal	70	86.4	9	11.1	1	1.2	1	1.2	81	100.0
Meningovascular	118	79.1	21	13.1	3	2.2	5	3.6	150	100.0
Vascular	32	64.0	13	26.0	1	2.0	4	8.0	50	100.0

Arsenical Treatment Preceding Tests—678 Cases.

									Total Number	Total Per cent.
Tabes	241	53.5	148	32.7	30	9.0	12	2.8	451	100.0
Paresis	150	86.7	18	10.4	4	2.3	1	.6	173	100.0
Taboparesis	41	71.9	13	22.8	1	1.8	2	3.5	57	100.0
Meningeal	61	72.6	23	27.4					84	100.0
Meningovascular	64	68.1	21	22.3	5	5.3	4	4.3	94	100.0
Vascular	31	31.6	11	19.7	3	13.3	9	21.3	57	100.0

Data adapted from ( ) Cooperative Clinical Studies in the Treatment of Syphilis, Early Syphilis, Ven. Dis. Inf. Reprint 41, 1932.
(b) Cooperative Clinical Studies in the Treatment of Syphilis, Asymptomatic Neurosyphilis, Ven. Dis. Inf. Reprint 62, 1937.
( ) Symptomatic Neurosyphilis, Kierland, O'Leary and Vandoren, Ven. Dis. Inf. 23:360, 1942.

full interpretation of seronegative latent syphilis and of the condition of patients in whom the diagnosis of syphilis, while supported by darkfield or clinical evidence has never been verified by serological test. Equal emphasis should be placed upon the positive necessity for a spinal fluid examination of all patients whose supposed state of latency has been diagnosed by the strongly positive blood serological test. Never under any circumstances, should a positive blood test for syphilis be slurred over or minimized (see page 30) The least that it demands once the possibilities of laboratory or biological nonspecific error are eliminated is an examination of the spinal fluid Only in this way will it be possible to detect the red flag at a time when treatment may yield arresting or curative results

Fig 51

A REMINDER—THE ADEQUATE SPINAL FLUID EXAMINATION

1 Observations on pressure color physical properties, when drawn.
2. A fresh fluid, 8 to 10 cc. in amount if obtainable, free from even microscopical blood.
3. A prompt cell count on the fresh fluid after shaking
4 *A quantitative Wassermann reaction. Precipitation test optional as yet.*
5. A protein test.
6. A reliable colloidal test gold, benzoin, mastic
7 Mailed specimens yield unreliable reports on cell counts and colloidal tests.

Refuse to accept incomplete reports on adequate specimens
("Wassermann positive," etc.)

The Luetin Test.—This cutaneous test proposed by Noguchi now belongs definitely to the past of diagnostic syphilology although its probably important immunity relations still deserve further study At the outset the nonspecific element in the cutaneous allergic phenomena of late syphilis was not appreciated, and interpretations involving it were presently seen to have an insurmountable margin of error Moreover it appears that luetin tests performed with suspensions of cultivated *Spirochaeta pallida* do not appear to give as trustworthy results as do those performed with organisms in suspension with tissue extract such as lung, liver and testis. The more recent publications of Hollander Kolmer Brandt, Gandy and Ambler and of Bessemans (1933) may be consulted by those desiring first-hand information In view of the equivocal and unfavorable reports, organic luetin was refused acceptance for N.N.R. by the Council on Pharmacy and Chemistry on the ground of insufficient evidence of value or safety

CHAPTER V

THE FUNDAMENTAL PRINCIPLES OF TREATMENT

Complexity and the Fundamentals.—The disposition to avoid a section headed "Principles" and to thumb the pages of a presentation until one reaches the routine prescriptions systems and schedules of dosage and intervals which it is fondly imagined will give the desired "practical knowledge of treatment" is one of the most serious mistakes in dealing with the therapy of syphilis that can be imagined.

The therapeutic formulas most widely accepted today are literally in the dust heap tomorrow and large blocks of text are dead before they are born. Witness the transformations involved in the efforts to shrink treatment for early syphilis from 05 weeks to 5 days. In such a rapidly changing field only principles remain to save the distracted doctor's sanity. The chief difficulties in the practitioner's management of syphilis have been found to consist, first, in a relative ignorance of drugs and complications; second, in the tendency to monosymptomatic treatment, especially as exemplified in the ruthless attack upon the positive Wassermann reaction as such; and finally in a tendency to indiscriminate bombardment, as when a mouse sets off the barrage of guns in a wild-animal trap. Unfamiliar with drugs and their dangers, with the purpose for which each is to be used, with the importance or insignificance of the symptoms first presented, and possessed with a laudable desire to do all that duty demands and the patient can pay for, tempered by an unfortunate disposition to stop when lesions heal or surface signs disappear, it is small wonder that the practitioner's treatment for syphilis has in the past decade been a monument to inadequacy early in the disease and to therapeutic furor and overenergetic misapplication in the later phases.

Therapeutic Experimentalism and Impressionism.—The very nature of syphilis sets conditions upon advance in knowledge which the practitioner cannot meet. Years of observation are required for the determination of a therapeutic result. Rigorous controls must be set which even the best organized clinics find it very difficult to carry through. The mere healing of lesions or the momentary betterment of the condition of the patient, instead of symbolizing a lasting and satisfactory therapeutic result, may be only the threshold to failure or disaster, as in the modern problem of Wassermann-fastness, of neurorecurrence and of therapeutic paradox. It is, therefore, particularly unwise to encourage the individual physician with a small experience and a small clientele in the disease to strike out for himself, disregarding precedents and the more massive experience of organized groups and centers of clinical and experimental investigation. Equipped with the principles which these centralized investigations offer him, he can be an invaluable aid in the determination of long-range results through the intimacy and the prolonged character of many of his contacts with patients. On the other hand, his opportunity to serve in this way is reduced to insignificance by the harm he can do

For those interested in the historical philosophy of treatment problems in the United States, reference should be made to pp. 186–189 of the second edition of this book.

Brown that the currently used trypanocidal test for arsphenamine therapeutic efficiency is not satisfactory as test of spirillicidal activity

All these considerations taken together seem to us to indicate strongly the need for stringent disinterested regulatory supervision of products used in the treatment of syphilis. The National Institute of Health of the United States Public Health Service which is responsible for toxicity standards in this country has thus far felt itself unable to take up the problem of therapeutic control.

Clinical Testing of Antisyphilitic Drugs.—It may perhaps serve the useful purpose both of defining the conditions under which drug testing in the syphilological field should be done and impressing the reader with the complexity of the problem, the need for controls and the slowness with which results can be evaluated, if we summarize here in tabular form more than decade of experience in testing drugs in the treatment of syphilis, together with impressions gained from conversations with authorities on various aspects of the problem.

1 The originator of preparation for the treatment of syphilis should be prepared to stat the composition and general method of manufacture to the clinician and responsible agencies that he approaches, though at the outset this may be done in confidence.

2. The first one to t years of the li history of an adequately studied syphilotherapeutic agent are spent in animal studies. Those relating t curative effect are, of course, the most laborious, protracted and expensive. Animal investigations include (a) animal toxicity tests by various routes of administration which should have been made and the results stated in writing before clinical trial is considered (b) reactions which should have been studied in animals, including effects on the skin, the vital organs and the eliminative mechanism, as well as the injected site if the drug is given intramuscularly ( ) the trypanocidal index should have been obtained, if the drug acts on these orga isms (d) spirillicidal effect, if directly observable, should have been studied in rabbits (e) optimum dosage and therapeutic indices should have been determined; (f) healing effects should be studied (g) curative action should be determined, not by single set of short-lived experiments, but by multiple animal passages through several generations, using the modern laboratory devices of lymph node transplant, emulsions and organ hash.

3. While these studies are in progress, stability of the drug under market conditions should have been observed and loss of therapeutic efficiency proved or negated.

4 The first test on man should begin with ( ) the definition of the field of application of the drug (for instance, tryparsamide in neurosyphilis as distinguished from an arsphenamine in early syphilis) (b) the originator and staff should test the toxicity for man of the first doses upon themselves, ( ) decision as to the amount and character of clinical material required should be reached early and studies should not be made by individuals or clinics insufficiently supplied with the necessary clinical material.

5 No other preparation should be used simultaneously with the drug under test. This requirement greatly increases the difficulties of clinical testing, because it is well recognized as an improper use of human material and an abuse of the Public Health responsibilities to test alone for example nonspirillicidal drug on considerable series of patients with early infectious syphilis (chancre and secondaries) except under strict quarantine and hospital control.

6 Adequate medical appraisal of the *status praesens* of all human subjects with proper and complet records must be vailable t the start. Observations must be made on reactions t administration both local and general.

Further observations should include studies of

7 The rate of disappearance of organism from active lesions.

8. Healing and symptomatic response

9 Rate of reversal of serological reactions in early syphilis, latent syphilis and other special aspects.

10. Therapeutic shock and flare-up.

11 Therapeutic paradox.

12. Serological relapse on blood and spinal fluid.

13 Clinical and especially infectious relapse.

14 Proportion of serologically resistant cases.

15 General tolerance of treatment.

16. Elimination, storage and penetration studies ma

17 Optimum dosage nd interval in man

18. Proper duration of treatment in man.

19. Reestimation of the field of application and of risk of reaction in man.

20. Correlation of results in animals and man.

21. Annual routine reexamination of treated patients. This necessitates extraordinary and rarely available follow-up facilities. The time required for adequate study of a preparation ranges from ninety days (to determine surface spirillicidal action) to the second decade and longer (to determine ultimate curative action).

22. No citation of results or exploitation of drug without clinician's approval based on reports at intervals, say of two, five and ten years.

23. Submission, in the United States, to the Council on Pharmacy and Chemistry after the second year and to the United States Public Health Service before tests on man are begun.

24. Consideration and solution, if possible, of those special problems and difficulties inevitably concerned especially with drugs acting upon the resistance mechanism rather than the organism (no spirillicidal effect).

This may be concerned as a rather idealistic program for controlling the use of drugs in the treatment of syphilis. It is perhaps safe to say that very few preparations in common use today would have survived such complete investigation or have, indeed, ever been subjected to it. It represents, none the less, an ideal to strive for and one applicable without too great difficulty to practically all preparations where the motive underlying their exploitation is scientific and humane rather than commercial.

Principles and methods of evaluation of antisyphilitic treatment are further discussed by Moore, Hardy, Robinson and Eagle (1936), Snodgrass (1938), Stokes and Beerman (1937), Eagle, toxicity-dosage relations (1944), Stokes, intensified treatment (1942), and Stokes, Beerman, and Wammock (1945).

PHYSICIAN-PATIENT RELATIONS AND PROBLEMS

Appraisal of the Case.—Before treatment is begun, not only is it necessary *to know with certainty that the patient has the disease, but it is essential to* know in exactly what way he has been affected by it. Not only must he be appraised as to his present status, but his possible therapeutic response must be carefully evaluated and his ability to tolerate ideal procedure, or various compromises with it from the standpoint of complications, must be carefully considered. Incomplete examination is the curse of syphilological treatment as it is of diagnosis today. Too often the physician, proceeding on the basis of a single suspicion-arouser, such as the positive blood Wassermann reaction, gives a heavy dose of one of the most powerful drugs in existence. Suppose there is a sluggish pupil that he did not see or a buzzing ear that he did not ask about? In a few hours the patient is perhaps in convulsions or deaf for life, perhaps he is merely anuric or paraplegic. Perhaps, to descend to the minor frequencies in accidents, he just vomits and can't stop, or has a chill, a high fever and a rash, and repeats the performance time after time until the discouraged physician calls the detail man in consultation or sends the drug supply back to the manufacturer with angry words. Perhaps, with a silent resolve, he falls back on "mixed treatment," not realizing that that is precisely what he has been using from the start. The specialist himself can with good reason speak apologetically and with humility of this inevitable problem of the correct appraisal of the case. He well realizes how frequently he himself falls to meet the full demands of conscience and sound practice in this regard. If one who devotes the larger part of his time to the problem must more than once take himself to task for some unrecognized though obvious fact in the patient's make-up that could have been identified by examination but which he has overlooked, how much more frequently must the harder pressed practicing physician, the specialist in other fields and the physician who for one reason or another must "take a stab at it," fail to live up to his first and most essential requirement. No matter how a syphilitic infection is recognized

whether by a complaint of falling hair an accidental or a routine discovery of a positive blood serological test, a "hot spot" in the family history or a thumping aneurysm presenting through the sternum—the patient must be examined and examined from crown to sole Only in this way can we decide what he needs on the basis of what he has and whether or not he can take it

Weigh the Risks Against the Benefits.—There are risks so serious, especially in the treatment of late cases by intensive methods, that the patient should not be asked to take them. There are benefits so doubtful and methods so double-edged that a hairline judgment can very properly be drawn between the decision to do or not to do It is not infrequently very much better syphilology to withhold than to give a drug, to prescribe rest instead of action and to adopt slow methods instead of fast ones. The ability to resist the spell binding effects of an arsenical miracle is sometimes the real mark of the expert though such a statement must not for a moment be taken to advocate the withholding of an arsenical in the field of its proper and most vital effectiveness, which is particularly the treatment of early syphilis and the control of infectious lesions.

Estimate Impairment and Tolerance—Throughout all of late syphilis the problem of individualization, again to be mentioned can be responsible in its misinterpretation for endless discredit and discouragement in the application of modern therapeutic methods. This is especially true in cardiovascular and neurosyphilis, and visceral, *vide* hepatic disease. It cannot be too frequently reiterated that to consider the capacities as well as the incapacities of the syphilitic patient with respect to treatment is almost the alpha and omega of the late therapeutic problem.

The patient s tolerance of treatment for syphilis has, of course many individual elements and fortunately rests upon a broad base of general ability to receive and profit by almost any even halfway intelligently directed therapeutic measures. Lack of tolerance under the guise of idiosyncrasy is an inescapable problem but it too frequently involves not only the inborn incapacity of the patient but the acquired intolerance that results from misapplied overstrenuous and ill-considered therapeutic measures. The invoking of "idiosyncrasy" to explain bad therapeutic results is a habit into which the most conscientious can easily slip and one which should never be indulged without the most searching self-examination for recognizable and avoidable mistakes in treatment methods. It should be widely understood that there is a way around or a means of forestalling most difficulties in syphilis therapy

The Time Factor—In weighing risks against benefits and even more in deciding upon an objective, the time factor in dealing with syphilis requires constant and reiterated emphasis. When the duration of the infection in the individual case can be ascertained or presumed it becomes an important element in decision as to the required intensity and duration of treatment This is particularly apparent in the effect of time on infectiousness. A patient whose disease is of more than five years duration need rarely if ever be treated by a technic directed solely at the prevention of infectiousness. It is therefore *ipso facto* possible to consider him more as an individual than as a social problem Again one of the serious mistakes of an era of arsphenamine enthusiasm has been the tendency to feel that a syphilitic infection of short duration is more easily cured and requires less treatment than one of a long duration This is the basis of the old concept of abortive cure in early syphilis that has been responsible for much Wassermann fastness, relapse late cardio-

vascular and neurosyphilis. A syphilis of fifty years duration may yield completely in symptomatic response for the remainder of life under treatment which, if applied to a syphilis of six days duration might result in almost unconquerable complications and ultimate disaster

The Age Factor —Experience with the biology of the disease leads to an appreciation of the age factor in a syphilitic infection This amounts practically to an appraisal of the average rate at which an untreated or partially treated syphilitic infection may be expected to produce symptomatically recognizable complications A man of twenty five, who at eighteen had acquired a syphilitic infection would be definitely in the period during which cardiovascular complications, while asymptomatic, could be expected to be in process and to be feared The decision as to the intensity of treatment to be applied in such a situation is based on a life-insurance-like appraisal of the years during which this patient will have the opportunity to suffer from progressive manifestations in this group of structures. It will *ipso facto* be more intense than the treatment of a man acquiring a syphilitic infection at the same age but recognized as absolutely free from symptoms two decades later These considerations are discussed in greater detail under the problems of latency

Therapeutic Shock.—The combination of powerful drug and uninvestigated patient most frequently resolves itself (let us say in one third of reacting cases) into a type of therapeutic explosion with which the practicing physician even today is all too unfamiliar This form of treatment complication or perhaps better therapeutic reaction has been spoken of as the Jarisch Herxheimer effect.

It was first described by Jarisch in 1895 and elaborated in conception by Herxheimer and Krause in 1902. The original effect was observed in the use of mercury injections and consisted in brightening or flare-up of the syphilitic roseola. Jadassohn, in 1895, and Finger in 1910, gave confirmation, the latter observer first noting the much more striking effect of arsphenamine as source of such reaction.

The term "therapeutic shock" used throughout this work impersonalizes the observation but emphasizes its potential gravity and significance, which are often paramount in the later stages of syphilis and in the involvement of vital structures in which local edema and reaction can have serious and even fatal consequences.

The earlier emphasis in discussing this reaction had been mainly upon the flare-up of cutaneous manifestations and the provocative serological response which has been interpreted as phase of the Jarisch-Herxheimer reaction. Only within recent years has it been realized that therapeutic shock takes place in any and every structure involved by syphilis at ll stages of the disease and that it becomes practical therapeutic problem only with the arsphenamines and at times bismuth. Whether or not shock results from the liberation of toxins from destroyed organisms or by irritation of living organisms before their destruction, cannot be regarded as fully established; but the occurrence of the reaction with drugs whose effect is not primarily or rapidly spirillicidal and the occurrence of provocative effect in test involving very probably lysis of spirochetes, seem t support either view the predilections of the interpreter may dictate Illustrations of "Herxheimer effect are given in Figs. 85 to 86.

Prevention of Therapeutic Shock.—Therapeutic shock effects are produced primarily by premature use of the arsphenamines and by overdosage with them. A safe general rule for their prevention in early syphilis, where they are least serious, is to make the initial dose of an arsphenamine never greater

than half the established maximum therapeutic dose In the presence of special symptoms from a particular group of structures such as the eighth nerve the recognition of an early neurosyphilitic involvement and in all late aspects of the disease therapeutic shock is avoided by the device of 'preparatory treatment' or 'preparation' which consists in the initiation of treatment with a slow-acting, relatively nonspirillicidal drug such as mercury or bismuth The length and character of such a preparation are discussed in detail under the chapter devoted to the heavy metals (p 220) *It should* not be understood that heavy metals never produce therapeutic shock, or that arsphenamines cannot be used without producing it. There is some reason to believe that drugs such as bismuth may produce a very appreciable and even serious degree of shock in some cases, and there is no doubt that the arsphenamines, in suitably low and slowly increasing dosage and by a route like the intramuscular which makes for slower absorption can be used without the induction of an appreciable degree of therapeutic shock.

The practitioner should make an effort personally to acquaint himself with this reaction, which comes on usually within the first twelve to twenty four hours after intravenous medication in an early case, by observing the course of the secondary eruption at the named time intervals and taking the temperature of the patient at two-hour intervals in several instances in order to detect the systemic phase of the reaction Delayed shock effect can be observed particularly well in bone lesions and in the symptomatic flare-up of neurosyphilis that occurs from one to four or five weeks after the institution of an intensive form of treatment in late cases. Local edema with systemic and symptomatic exacerbations is the essence of the reaction at all sites and while of no great significance in a chancre, it may be fatal in the wall of a coronary artery or the pinhole opening of a larynx occluded by a gummatous process

Therapeutic shock is, of course familiar in many other conditions besides syphilis, including reaction to tuberculin, t -my and to nonspecific therapeutic measures. The great complexity of the mechanism involved and the *fact that certain of the manifestations, particularly those* associated with hyperemia, have no necessary connection with the medicament or even with the organism concerned, is suggested by the critical and stimulating summary of Bettmann. A reflex vascular mechanism is pparently involved and Böhme called ttention to the accentuation of dermographism which may form part of the process Bohme confirmed and reemphasized Böhmig observation. Böhmig believes the Jarisch-Herxheimer reaction to be an anaphylactic response t antisyphilitic drugs. Matzenauer and also Oppenheim have pointed out that while the Jarisch-Herxheimer effect may be regarded in general as f vorable type of reaction approximating therapeutic inflammation, severe Herxheimer effects produced by overdosage sometimes have deleterious instead of beneficial influence. The importance of possible temporary or permanent vascular injury or hypersusceptibility involved in therapeutic shock may explain the clinical impression that patients subjected to severe therapeutic shock run thereafter stormy course with respect to vascular reactivity dermatitis and the like under subsequent arsphenamine treatment. Milian has recently reiterated his belief that the Jarisch-Herxheimer reaction is form of therapeutic activation of the disease process by the drug employed, and that it should not be made the signal for reduction in subsequent dosage. Houghton has shown that the Kahn reaction in early secondary syphilis, quantitatively measured, parallels the flare-up in the secondary eruption, the range of increased intensity being from 60 Kahn units to 240 Kahn units, following 0 4 Gm. of arsphenamine. He opposes Milian view that the aggravation of clinical symptoms is due to insufficient therapy and believes rather that it is due to liberation of endotoxin from destroyed organisms.

Therapeutic Paradox.—The intense action, particularly of the arsphenamines, produces not only therapeutic shock but a rapidity of healing which

has disadvantages sometimes far exceeding any possible advantage. In early syphilis, rapid healing provided it be accompanied by adequate spirillicidal action, is ideally desirable. In late syphilis rapid healing is tantamount in many cases to a high degree of fibrosis and replacement of organ parenchyma which may have the most serious effects. It was presumably with such considerations in mind that the original directions for the use of arsphenamines, as pointed out by Wile, contained explicit cautions against the indiscriminate use of the drug in late syphilis of the visceral and cardiovascular apparatus. To Wile belongs the distinction of having formally revived these cautions after a decade of indiscriminate enthusiasm and to have pointed out the seriousness of what he has called therapeutic paradox as a general problem of treatment.

A typical example of arsphenamine therapeutic paradox appears in the treatment of syphilitic cirrhosis of the liver. The patient with a markedly enlarged, diffusely involved cirrhotic liver but showing no evidence of portal obstruction, is placed at the outset on arsphenamine treatment, and makes an initial rapid response with improvement in general condition and marked reduction in the size of the liver. This therapeutic gain, however, is too often shortlived. Presently the patient begins to lose ground, the shrinking of the liver by the rapidly developed fibrosis is accompanied by obstruction of portal circulation, ascites appears and serious complications, with perhaps an ultimately fatal outcome, too often ensue. In a case of this sort the rapid healing effects have so seriously interfered with the circulation and function of the liver that by virtually reducing an important viscus to a mass of fibrous tissue, the drug has killed the patient while curing the disease. In coronary and myocardial involvement the rapid advance of myocardial fibrosis and embarrassment of circulation by coronary occlusion is one of the distressing sequels of the too ready use of arsphenamine in syphilitic cardiovascular disease. Deschweinitz has repeatedly emphasized the damage done by fibrotic healing under arsphenamine treatment as applied to ocular syphilis.

Prevention of Therapeutic Paradox.—The remedy for the complication is directly apparent from the logic set forth. In Wile's own words, "Treatment directed to a diseased organ in which the inevitable and ultimate result, both of the disease and of the treatment, is the production of a scar, should be of the type which leads to a slow rather than a rapid process of healing. It seems injudicious to employ in the treatment of any form of syphilitic disease any form of therapy in which the ultimate process of the disease is rapidly anticipated, so to speak, by the effects of the treatment. A gradual resorption seems to result in a better-functioning organ than follows a rapid absorption and disintegration of the disease processes. Such gradual effects can be obtained with mercury and iodide, with the careful use of bismuth and by the arsenicals in greatly reduced and graduated dosage, precisely as in the avoidance of therapeutic shock effect. In other words, postponement of the arsphenamines and the use of preparatory treatment will do away with two of the most serious sources of bad results with which the physician who treats late syphilis must deal.

Envisage an Aim or Objective.—Having examined the patient, and having detected and appraised, so far as possible, his impairment, his tolerance and his susceptibility to therapeutic shock and therapeutic paradox, a conscious, clear-cut effort should be made to formulate the purpose of treatment and to consider the methods best adapted for achieving the end desired.

Intuitive and Experiential Factors.—It is always hard to realize that our vision of what is really happening under treatment is indirect and subject to unknown correction in terms of peculiarities of host and organism, for which we have no means of measurement or detection.

We expect standard results for standard amounts of treatment, as if we were carving block of know hardness with tools of known edge. Instead, we obtain central group of good results, margin of medium results, and a fringe of failures which, when seen in itemized form, looms large. The trend of improvement in treatment methods is less toward sharp-cut cures and failures and more toward increases in average efficiency The syphilologist often evaluates the combination presented by his patient and the organism with which he is infected, in the course of the first few months rather than days of treatment. His intuitive estimate of the situation is often the best background for anticipating and forestalling trouble. He learns to recognize the "mucous membrane relapser the "meningeal relapser the man who thrives on rubs, the patient who easily overtreats, the patient whom nothing can harm, the irritable skin, the phobic mentality and the resistance that nothing can budge These are the priceless assets of experience. The patient who shifts about from one physician to another intolerant of supervison, may lose the benefit of any coordinated and balanced comprehension of his case.

The first decision which must be made in the majority of cases is that of "cure" *versus* arrest. The objective in a youth with a three-day old chancre is completely different from that of the elderly tabetic with ataxia, lightning pains and incontinence. The most striking contrast exists between the ideals and methods of early as distinguished from late treatment and between massive as contrasted with symptomatic methods. A selection of drugs and a technic entirely appropriate to a latent infection with no physical signs to support a positive serological reaction, may be fatal, if applied to a patient with only trifling aortic signs, but the well-defined beginnings of an angina pectoris. The mere difference in the spirillicidal effects of bismuth and neoarsphenamine a matter of less than a week in rate of disappearance of organisms has been blamed in part for an increase of syphilis in France in contrast with its decrease among her neighbors. Innumerable complexities arise in consideration of the influence of treatment on resistance and the disturbance of defensive balance by injudicious and incomplete therapeutic measures The weighing of therapeutic decisions involves not alone the patient himself but the social order his economic and personal status, his habits and his family and friends Errors in judgment, at times apparently not particularly concerned with the individual patient's individual syphilitic involvement, lead, as in the exacerbation of paresis under tryparsamide therapy to the discredit, in the eyes of the inexperienced and uncritical, of the entire fabric of the modern and demonstrably effective control of the disease. Through study of the case, through reading and through consultation the reasonably equipped physician can satisfactorily decide many of these problems for himself provided he recognizes the obligation and makes almost a ritual of its performance It is not too much to say that there is a modern technic whose effectiveness can be expected to range from 50 to 100 per cent for the achievement of every practical therapeutic aim in connection with the disease. To refer the matter to hearsay or to the instructions on the drug wrapper may lead to a catastrophic *dénouement*.

At this point ttention may properly be called to the invaluable abstracts published monthly by the United States Public Health Service in the journal "Venereal Disease Information, subscription to which, at nominal cost, may be made through the Superintendent of Documents, United States Government Printing Office

System *vs.* Individualization.—The trend and experience of the modern public health movement against syphilis seem to be unmistakably toward the recognition of a highly significant principle in syphilotherapeutics Incline to system early and to individualization late." From the League of Nations

and Cooperative Clinical Group studies it will be apparent that practically hard-and fast routines can even be employed in the management of large numbers of patients with syphilis both early and late. Reasonably accurate comparisons between the results of these systems and a process of standard ization which should lead to an ultimate optimum for the drugs available to this generation may be achieved The comparative youth of patients their general good health above all their freedom from the complicating and qualifying disabilities for which syphilis, the wear and tear of life and other diseases, are responsible in their later years, all combine to make the management especially of the primary secondary and latent phases of syphilis more or less of a machine affair conforming closely to certain standards and redu plicable from clinic to clinic and office to office throughout the world

The Organization of Treatment—Clinic *vs* Doctor —The syphilis clinic or other agencies for mass treatment publicly or privately operated are the obvious and natural answer to the growing complexity of syphilis treatment and the evident instrument for system and standardization Simplification, on the other hand tends to the distribution of any form of diagnosis and treatment among the large body of practitioners While the issue as thus drawn applies perhaps to the entire field of medicine in the problem of venereal disease it is acute Here the individual practitioner is now on trial as nowhere else in medicine and nowhere is his dominion harder pressed or more gravely threatened.

The treatment of syphilis in private practice is gravitating into the hands of a limited group within the general body of practitioners. In this group, constituting perhaps 10 to 15 per cent of the physicians of this country lies such hope as exists for an American solution of the problem of venereal disease control dependent upon the individual rather than state or corporate initiative

The Advantages of the Clinic.—By the use of technicians under direction, the clinic can surpass the average physician in technic. If and when foreshort ened intensive methods and fever therapy are widely applied, syphilotherapy will be increasingly centralized and institutionalized Centers can surpass the average physician in physical facilities for a complete examination and appraisal though in the individual case they will rarely except under super human inspiration equal in detailed perfection the decisions of a highly trained expert. For a certain impersonal quality of service and for its short comings in judgment, the clinic can offer the economic advantages of cost lowered by business methods and mass production. Through the use of the same economies it can spend where the practitioner unaided cannot, and can follow the patient maintain scientific record of him and from large series of cases, tests or repeated therapeutic manipulation evaluate in a short time the worth of procedures which the individual cannot determine from less than a lifetime of work in the field Even allowing for an indefinable something which reduces the level of performance of the individual as a cog somewhat below that of the individual acting on his own initiative and on his undivided responsibility we are satisfied from our own observation that the reasonable demands of the movement for the control of venereal disease with respect to syphilis can be met with sufficient completeness for the ultimate extinction of the disease by organizational treatment both in public and in private practice

The Expense of Treatment.—Expense from the standpoint of the patient, is one of the most serious issues in elaborating the treatment of syphilis under

the demands of modern knowledge. Most patients at the age when they acquire the disease are penniless at the foot of the ladder of business and professional success. Years later confronting one of the late complications of the disease, they may have reached the bank president s desk or the financial status of a captain of industry but in the days when effective treatment would have insured their future from the health standpoint, they had neither the free time nor the money for curative management. It is therefore a definite obligation upon the physician at large and upon the syphilotherapist to try to think preventively for the patient in terms which are compatible with his purse.

It is here that "production methods capture the field. For about one dollar per patient visit, a reasonably well-organized clinic for dermatology and syphilis can provide better grade of care than the average doctor can give t $5.00 per visit; and for the cost of the serological tests alone in strictly privat practice clinic can supply the entire three years of the most modern management of syphilis and more than meet the cost of all its services. Analyses of the cost factor have recently been published by Keidel, Bromberg and Davis, Thompson and Brumfield (1936) Goldberg (1938), Brumfield (1939) Beerman (1940) Cornelz (1940) and others. As Stokes has repeatedly said elsewhere syphilological private practice nowadays is literally so far as the early stages of the disease are concerned, capitalizing privacy not performance Even privacy our last hold on the taboo-ridden public, is being endangered by the well-planned equipment hich the modern clinic can furnish. Organization is inevitable in venereal disease control and it remains to no small extent for the physicians responsiveness and interest in the movement t keep him at the head of instead of t the mercy of organization when it assumes its place i the field. I the place therefore, of mere blind opposition and distrust, it is strongly urged on physicians confronted by the encroachments of organized zeal, that they join rather than denounce; and from within, not from without, by constructive cooperation rather than mere indignant opposition they leaven the lump and mold the policy to the conservation of the values of personal and individual medical practice.

The so much *feared* assumption of complete authority and responsibility by the state in the venereal disease field has at least, thus far in this country been more a bugaboo than a fact. Certain functions which the state can easily perform for the practitioner not only constitute no invasion of his individual prerogative but, if refused by the physician, will ultimately lead to his actual replacement for inefficiency Nothing would seem more unwise than for the *individual doctor to refuse to go halfway to meet the state in the working out* of a joint solution The tendency of American public health authority has been to lean over backward in avoiding encroachment on the practitioner s field rather than the reverse and the doctor who rejects the opportunities afforded by the state for protecting and developing his syphilotherapeutic technic, has only himself to blame if he is ultimately replaced What might be denominated "*legitimate functions of the state in present American practice* are considered in the closing chapter

The Use of Consultation —The actual technic of treating syphilis vexatious and even difficult as it sometimes is can be mastered by the majority of practicing physicians and by most medical students in their hospital and intern contacts. It is quite a different matter however to master the general knowledge of the disease *which should underlie many therapeutic decisions* so that there is a definite place in clinical syphilology for what might be called the consultant prescription, especially as applied to late syphilis

The volume of question and answer material on yphilis alone, passing through such department as "Queries and Minor Notes in the Journal of the American Medical Association is evidence of the growing ppreciation by the profession of the need for some form of consultant

service The attempt to answer the questions of physicians seeking consultation by letter in behalf of patients very quickly demonstrates the wide range of problems involved. (See Stokes, Ingraham and Stannard "Two Thousand Questions 1940.) Correspondence is at best only a relatively unsatisfactory medium. The information supplied with the question is often insufficient for the answer which is desired and even when supposedly full information is supplied, it contains serious gaps as, for instance the omission of a colloidal test formula, the presence of blood cells in the spinal fluid, and items regarding the eyegrounds, all of which may be vital to the decision desired It should not, therefore, be imagined that any column or question-and-answer-bureau type of response to the need for consultation in syphilology can be satisfactory or at all substitute for the personal examination of a properly organized special center or individual specialist.

The range of examination necessary in late syphilis is moreover so great that it is *ipso facto* out of the question to study the case properly without facilities rarely available to any one individual. Recognizing this fact, there had developed in Germany at the close of World War I a definite network of consultation centers ("Beratungsstellen"). Centralized facilities are fundamental to the British program and are likewise essential in Scandinavian organization, the oldest and, on the whole the most successful in the world. The great Central Institut in Copenhagen contains a register of all the patients in the country who have syphilis. The United States Public Health Service offered its service to the profession for the evaluation of patients at any of its clinical centers in 1941 Central registries equipped with adequate tabulating machine systems both for the registration of venereally diseased patients, more specifically syphilitic patients, and for the control and check on the practice and follow-up of clinics are being installed in a number of important centers, with the aid of the United States Public Health Service. While as research instruments their efficacy is controversial, there can be no question of their value in the systematization of control of the clinic treatment of the venereal diseases.

Consultation by correspondence should be an important aid to the physician in private practice and Kroll (1943) has described the type of system developed up to that date in California, Connecticut, New York and West Virginia. An attempt to develop such a system in another state however met with a set-back based on the medicolegal responsibilities involved in prescribing treatment for a patient who has not been personally examined by the prescriber It was informally ruled that such procedure in a disease as serious as syphilis might constitute actionable malpractice. Problems of this sort will have to be ironed out by consultation between the legal and public health authorities concerned, and probably do not constitute a serious bar to useful service. The type of material handled and the questions involved in consultation by correspondence for syphilis were critically examined by Stokes, Ingraham Jr and Stannard on the basis of a ten-year collection of material including the consultation service supplied by the Journal of the American Medical Association through "Queries and Minor Notes. Up to 1940 the doctors' questions concerned in order of numerical frequency treatment schedules, the choice, properties, dosages, methods of use, and recommended preparations among drugs serologic tests and their interpretation, treatment reactions; case histories for diagnosis; and various problems involved in the differential diagnosis of syphilis. It was clear that the physician is more interested in late than in early syphilis; that he had little interest in and rudimentary conceptions of the problems of infectiousness, of pregnancy in syphilis, and of prenatal or congenital syphilis. Very few questions were asked concerning the spinal fluid, transfusion syphilis, and the use of the darkfield. By putting the personal touch and genuine consultant discussion into replies to query letters a very effective educational instrument can be made of them, and the cooperation between state and private practice greatly enhanced to the advantage of all types of patients. For details as to the mechanism involved in efficient service reference should be made to the above designated authors papers.

Possibilities and Limitations of Consultation.—The physician who seeks consultant direction in the management of a patient with syphilis should both expect and desire to have his patient completely reexamined by the specialist in accordance with a systematic schedule This arrangement is preferable to a fragmentary examination in which part has been covered by the physician and part by the specialist. The report made to the physician should give the complete examination results, the discussion of the meaning of the findings, and a clear-cut prescription for treatment procedure in which doses, time intervals, avoidance of complications reasonably to be expected and so forth, should be carefully detailed It is, however unreasonable for the referring physician to expect that such a prescription can cover a period much greater

than a year or that it can be extended indefinitely merely by subsequent correspondence or that an accurate description of the procedure to be followed can be made foolproof or impregnable against the defects of bad technic and unsatisfactory execution. As in the reduplication of scientific experiments in which it is part of the code to use the exact technic of the originator so in carrying through technical suggestions regarding the treatment of a patient, very slight departures from original instructions may have very serious significance. It is for this reason that the consultant prescription should take all reasonable account of difficulties that may be anticipated and instruct the physician who is to assume a direct responsibility in regard to all possible details. The physician should provide for himself a reasonable groundwork by reading accessible periodical and other literature.

Obstacles to Thoroughness in Treatment.—Rapidly achieved symptomatic results and the inconvenience of good methods constitute the two most serious bars to the thoroughgoing treatment of syphilis at the present day. A patient who fifty years ago lived with the outward evidence of his disease for weeks or months while a slow-acting regimen of mercury by mouth and the course of his infection gradually developed his natural resistance to the point where symptoms responded, is now relieved of all knowledge that he has syphilis within a few days. He can be held to an awareness of his condition only by the rather tenuous and unreal tie of a blood test, which, after a few repetitions he regards as a new-fangled device for "keeping him coming." Colonel Harrison has called attention (personal communication) to the bad effect on treatment continuity of informing the patient as to the outcome of his earlier blood tests in the course of treatment. The patient has learned by hearsay to regard the negative blood test as the goal for which he is striving and the moment he learns that it has arrived, he steps out of bounds and vanishes.

Among other serious obstacles to thoroughness are the effects of pain and reaction in discouraging the patient, and of failure on the part of the physician to make a sufficiently close contact with the patient in the first two or three interviews to gain his confidence and educate him to his responsibilities.

Discomfort, pain and reaction are the present-day barriers to the control of syphilis. Colonel Harrison's experience in the British Ministry of Health, for example, leads him to oppose the use of spinal puncture as part of the procedure of a public health clinic because reaction and loss of employment become to his mind, so serious that the ultimate purpose of the system of venereal disease control is lost sight of—the treatment of the patient to noninfectiousness. In a survey carried out by Pugh and associates in the clinic at the University of Pennsylvania, it was shown that discomfort, especially from intramuscular injection, was apparently responsible for the second largest proportion of lapses from treatment, being exceeded only by failure to tell the patient the facts of the disease with sufficient emphasis.

Referring to the vital importance of the first contact with the patient in insuring continuous and cooperative response, I know of nothing which is harder for us to do than to take the time needed to meet our responsibilities in this particular. Our students are compelled to memorize and recite the substance of the first interview with a syphilitic patient, for there indeed the future of the disease is more often determined than anywhere else. We have not found the spinal fluid examination to compare with either the factors previously mentioned or with a number of others as deterrents to continuance of treatment.

GENERAL THEORY OF MODERN TREATMENT: THE FUNCTIONS OF DRUGS

The Mechanism of Chemotherapeutic Effect.—Even so recently as 1926 (first edition of this text) it was possible with a fair degree of conformity to opinion to describe for practical purposes the mechanism of drug therapy in

syphilis in terms of four items specific *versus* nonspecific effect, and spirillicidal *versus* resistance-building action. Current developments which have compelled the rewriting of this section indicate that the mechanism of chemotherapeutic effect in syphilis is far too complicated to be included in such a relatively simple schema. None the less, the terminology previously employed has the merit of teaching value and can serve as a guide to clinical practice without too completely violating the canons of experimental and scientific accuracy

The Parasitotropic Views.—A number of investigations have shown that the mode of action of one therapeutic compound upon two different types of organisms, or even upon two species within the same family may vary considerably and that compounds within the same group, as for example, the arsphenamines, may act in different ways upon the same organism. With regard to the action of the arsenicals, two groups of thought are apparent the older of which the theories of Schumacher are representative considered the action of an arsenical to be spirochetotropic and mediated through the oxidation-reduction mechanism of the living organism. Muhlpfordt regarded the effect of the arsphenamines as that of powerful reducing agents, and was in doubt as to whether the spirochetotropic effect was exerted by way of chemical reduction or as an actual action of the arsenic. Voegtlin, Dyer and Leonard, among others, supported the conception that arsenoxide, a decomposition product of the arsphenamines, was instrumental in the parasitotropic and parasiticidal effect of these drugs and that this action was mediated through sulfhydryl compounds such as SH-glutathione. The action of the introduced arsenic is therefore that of interference with the oxidation mechanism of the cell. Schumacher's most recent statement draws upon the lipoprotein mechanism and contends that the rapid lysis of spirochetes following an arsphenamine is the result of the liberation of lipoproteolytic ferments. Schumacher contends that the arsphenamine base is lipoprotein soluble is liberated by the carbon dioxide of the blood and is a powerful reducing agent which destroys the spirochetes as soon as it is bound to them, thus acting through interference with their oxidation mechanism. Eagle has recently (1938–1939) investigated the mechanism of chemotherapeutic effect by a series of *in vitro* studies controlled by animal inoculations. He demonstrated that the trivalent arsenicals and soluble bismuth salts exert a direct spirocheticidal activity in concentrations approximating those found in the blood after therapeutic doses of the compounds studied. This direct action was suggested by previous studies (Bronfenbrenner and Noguchi (1918) Schamberg, Kolmer and Raiziss (1917) Akatsu (1917), Weiss and Wilson (Kolmer) (1926)) but denied by Levaditi who believed tissue substances were needed for *in vitro* activity of the arsenicals. The spirocheticidal action is increased by increasing temperatures and little affected by serum. It is markedly inhibited by tissue derivatives and almost completely stopped by sulfhydryl compounds added in excess. Arsenoxide and bismuth compounds act in spite of removal of molecular oxygen, while the spirocheticidal action of neoarsphenamine, highly active aerobically is negligible when tested anaerobically because its action depends on molecular oxygen to form arsenoxide. Kolmer and his coworkers (1939–1940) almost simultaneous with Eagle showed the high spirocheticidal action *in vitro* of various trivalent arsenicals but were unwilling, because of variable factors, to consider *in vitro* action to be used as a measure of therapeutic effectiveness.

The Tissue-stimulation Views.—The contrasting view is well presented by Tryb. He opposes Lesser Blaschko, and Kreibich in their belief that the action of the arsphenamines is spirochetotropic and radically different from that of mercury which influences the defence mechanism. Tryb points out the many reasons for believing that at least a large part of the action of an arsphenamine is not upon the *Spirochaeta pallida* as such, but upon the organs and tissues of the body His theory thus tends to bring closer the conception of the action of the heavy metals and that of the arsenicals. It explains moreover some effects of nonspirillicidal arsenicals on syphilis. Briefly stated, Tryb maintains that following the use of an arsphenamine in secondary syphilis, for example the macular eruption disappears, not because the spirochetes are destroyed by the drug, but the spirochetes disappear because the drug has stimulated the tissue to a spirochete-destructive reaction A good deal of support for this more or less nonspecific view of the action of the arsphenamines is found in the accumulated observations on the rôle of the reticulo-endothelial mechanism in bodily defence Most of the observations on which these theories of organotropism and defence reaction are based, cite the great disparity between the antiparasitic action of the drugs concerned *in vitro*, and that *in vivo*. Amounts of the drugs too small to kill the microorganisms in the test tube are highly efficient when injected into infected animals. The clue to a possible rôle of the reticulo-endothelial system arose from observations on the storage of arsenical

drugs in the body following injection, for there can be no question of the influence of the reticulo-endothelial structures in storing arsphenamine. In the experimental infection of the mouse with recurrent spirochetes or trypanosomes, Kritschewski and Meersohn, and Feldt and Schott have shown that depression of the reticulo-endothelium by block procedures and splenectomy interferes greatly with the chemotherapeutic efficacy of arsphenamine compounds. Kritschewski and his associates therefore maintain that quick initial storage and gradual subsequent release of the drug by the reticulo-endothelial system contribute largely to the effect of the arsphenamines, the favorable effect of storage having previously been demonstrated by Voegtlin and his associates. Feldt and Eisenmenger have opposed Kritschewski and Jungeblut conception that the arsphenamine is oxidised to an effective parasitotropic oxide. Spirochetes proved t be much more resistant than trypanosomes in the presence of arsphenamine and arsenoxide, which perhaps explains the discrepancy between these uthors results and Voegtlin views on the importance of arsenoxide in spirocheticidal and trypanocidal effect. Kolmer Schamberg and Brown found arsenoxide-containing arsphenamines t be more spirillicidal than trypanocidal. More recent studies (Muir and Becker 1931 and Pfeiffer and Tatum) have thrown no new light on the rôle of the reticulo-endothelial system in chemotherapy

In spite of the obvious difficulty of reconciling these conflicting views the clinically observable rapidity of action of the arsenicals in destroying spirochetes in the active lesions of syphilis justifies pigeon-holing them as essentially the most potent spirocheticidal agents in modern syphilotherapy whether the action is exerted directly on the organism or through a powerful organotropic influence on some structure or group of structures in the defence mechanism of the body or both.

Turning next to the action of mercury and, in fact, of all the heavy metals including bismuth it appears that an effect much more distinctly organotropic or cellulotropic takes place with these drugs although Eagle has shown a direct action on the spirochete for soluble bismuth at least. It has been shown that the concentration of mercury for example, in the blood stream at the height of therapeutic effect is far too low to act as a direct spirocheticide (Sidlick, 1938) All the heavy metals share the peculiarity of producing their characteristic reaction, as has been pointed out by Levaditi and coworkers for bismuth as the result of storage of extremely minute amounts of the metals in the body cell Goldzieher and Peck, studying this action of mercury and of sulpharsphenamine on the reticulo-endothelial system, reached the conclusion that these two drugs stimulated the phagocytic activity of Kupffer s cells and suggested that antibodies might likewise be liberated through this action It may therefore be contended with reasonable conformity to recent conceptions, that the action of a heavy metal and particularly of mercury is conspicuously upon the body cells and that they are therefore the resistance-stimulators par excellence in spite of a demonstrated *in vitro* spirillicidal action (Eagle, 1939 Sollmann and coworkers) In their therapeutic use they require reinforcement for spirillicidal effect from the much faster-acting and spirochete-destroying arsphenamines The intermediate position between mercury and the arsenicals occupied by bismuth will be more definitely pointed out in the ensuing chapter on the heavy metals

Specificity *versus* Nonspecificity —Specificity is the term applied to those features of the action of a drug which are distinctive for syphilis and not shared by its general action on disease processes All the drugs in common use in syphilis except iodide have both specific and nonspecific effects. The more searching the analysis however the harder it becomes definitely to say just where specificity ends and nonspecificity begins in a disease with so distinct a nonspecific defence mechanism as syphilis. All the drugs used in the treatment of syphilis produce some effects which are general in character and not

Fig 55.

A SCHEMATIC COMPARISON OF THE TRIVALENT ARSENICALS, BISMUTH AND MERCURY

	Arsenical	Bismuth	Mercury
1	The most effective spirillicide	Also spirillicide	Practically not directly spirillicidal.
2.	Uncertain, probably minor influence on defence	Influence on defence intermediate	Major influence on defence
3.	Rapidly heals infectious lesions.	Too slow for public health purposes.	Does not control infectious lesions.
4.	Chief preventer of infectious relapse if adequately used.	An adjunct only in this capacity	An adjunct inferior to bismuth.
5.	Hence the critically essential drug in early syphilis.	Never use exclusively in early syphilis.	Totally inadequate alone in early syphilis.
6.	Used inadequately provokes allergic response and precocious tertiarism.	Allergic by-effects suggested by flaring of infections and provocation of mild eruptions	No allergy-inducing action.
7	Acts rapidly in all phases of syphilis.	Acts fairly rapidly	Acts slowly
8.	Provokes focal and general flare-up (therapeutic shock)	No recognizable therapeutic shock in ordinary dosage	No focal or general flare-up.
9.	Induces therapeutic paradox and healing fibroses.	Little or no paradoxic effect though suspected in hepatic and cardiac syphilis.	No therapeutic paradox.
10.	Hence dangerous at the outset in late syphilis of vital structures.	Safe at the outset in latent and late syphilis, but use circumspectly for heart or liver	Safe as preliminary treatment in late syphilis of any type
11.	Toxic for heart and blood vessels.	Low toxicity for vascular structures.	Low vasculotoxicity except in high total dosage
12.	Toxic for liver and skin	Low toxicity for liver and skin.	Low toxicity but greater than bismuth.
13.	Gastro-intestinal toxicity annoying not serious	Little or no gastro-intestinal toxicity	Marked serious gastro-intestinal toxicity early and late
14	Toxicity for mouth insignificant	Toxicity for mouth moderate, rarely serious.	Toxicity for mouth marked, consistent, often serious
15	Low renal toxicity	Low renal toxicity	High renal toxicity
16.	Marked nonspecific effects	Nonspecific effects uncertain but not marked.	Least nonspecific effect of all
17	Marked stimulant and tonic action.	Tonic effect good, not striking.	Definitely depressant, anemia, weight loss, malaise
18	Therapeutic efficiency often variable	Therapeutic efficiency varies with vehicle and salt.	Most stable and trustworthy, least erratic.
19	Contraindicated in certain blood dyscrasias (aplastic anemia)	No special effects.	Contraindicated in nonspecific anemias.
20.	Suited mainly for intravenous use.	Intramuscular only safe effective route.	Variety of modes of administration.

dependent on the fact that the patient is infected with the *Spirochaeta pallida*. The gamut ranges all the way from mercury, which is the most specific for syphilis (i. e., has the least important general effect on disease processes other than syphilis) to iodide, which is but little specific for syphilis (i. e., has the most important and extended action on other conditions and the least distinctive effect on syphilis). In many important aspects of syphilological work, as, for instance in the performance of therapeutic tests, it is constantly necessary to bear in mind the specificity of the agent employed in the test in order to interpret properly the response.

Fig. 56.

COMPARISON OF SPECIFIC AND NONSPECIFIC ACTION OF MEDICATION FOR SYPHILIS

	Mercury.	Bismuth.	Arsenicals.	Iodides.
Specific effects.	Marked stimulation of cellular (tissue) resistance to *Spirochaeta pallida*. Slight direct destructive effect on *Spirochaeta pallida*.	Same as mercury but more direct effect on organism.	Marked direct destruction of *Spirochaeta pallida* by chemical combination with organism either through an oxidation reduction mechanism or lipoprotein. Slight [illegible] y stimulation of cellular resistance.	None.
Nonspecific effects.	Formation of agglutinins and lysins. Action upon other processes with an infectious basis such as nonspecific periostitis, uveitis, etc. Intestinal antisepsis. Depressant effects.	I [illegible] ea l g use in other d [illegible] are nonspecific effect of bi[illegible]m[illegible]th (p. 180)	Formation of agglutinins and lysins. Possible reticulo-endothelial stimulation. Action upon other infectious processes including tuberculosis, lymphomas, uveitis, mycoses, etc. All these effects more marked than with mercury or bismuth. Destruction of intestinal parasites. Tonic effects of arsenic.	R [illegible] l l g effect on granu[illegible] l m t tissue in general.

Figure 56 presents a schematic summary of specific and nonspecific action in the field of drug medication for syphilis. No mention is made of fever therapy with its large element of nonspecific effect and its debatable specificity. A résumé of this sort should be used only with due regard for the still existing uncertainty in our knowledge of the action of the drugs enumerated.

Spirillicidal effect, even though its modus operandi as between direct attack on the organism and stimulation of body cells to phagocytize and destroy organisms is still under dispute, is a very real phenomenon clinically and forms the basis for the selection and emphasis on the trivalent arsenicals particularly in controlling infectiousness and dealing with early syphilis. This effect is conventionally contrasted with the action of mercury, which, by the ordinary methods of administration, is only very slightly if at all directly

spirillicidal. There is a good deal of reason to believe, however, that the lack of spirillicidal effect in the heavy metals, particularly mercury, is due to the limitations on dosage set by their high toxicity for the animal body. Bismuth, whose toxicity is markedly less than that of mercury, exhibits in the dosages which are possible in treatment a strikingly higher spirillicidal effect, and a rapidly absorbed soluble mercurial salt (i. e., the succinimide) given at frequent intervals because of the absence of storage effect, to be discussed later, can be shown to have spirillicidal action almost comparable to that of the weaker arsphenamines. Be that as it may, the practical issue concerns the securing of these effects in treatment and in that field it must be conceded that the arsphenamines and arsenoxides have an overwhelming advantage in spirillicidal action, that bismuth stands next, and that mercury brings up the rear with iodide apparently entirely devoid of spirillicidal action as such.

Clinical Demonstration of the Comparative Spirillicidal Action of Arsphenamine and Mercury.—The practicing clinician who uses the darkfield can determine for himself the spirillicidal activity of the drug which he employs in a qualitative if not a quantitative way by the periodic reexamination of secretions from a spirochete-containing lesion every three or four hours or even daily after an injection of the drug in question. In this way it is also possible to detect worthless and ineffective arsphenamine preparations and variations in individual patients' response to the drug. It must not be forgotten that observed variations in such tests may be due to the ineffectiveness of the drug quite as much as failure to respond on the part of the defence mechanism of the host (see treatment-resistant syphilis, p. 140).

Lévy, in a study in which bismuth and the arsphenamines were compared with respect to spirillicidal efficiency, found that the arsphenamines were four to sixteen times as rapid in their spirillicidal action as was bismuth. The neoarsphenamine used in Lévy's series caused the disappearance of spirochetes from a surface lesion, even in subtherapeutic doses, such as 0.15 Gm., within twenty-four hours in 3 out of 5 patients. With an initial therapeutic dose of 0.3 Gm. the spirochetes in 50 per cent had disappeared within twenty-four hours, in 38 per cent within two days and in 12 per cent within three days of its administration. It appears that the arsphenamines vary in the rate of their effect as do all drugs used in treatment. Even a water-soluble bismuth preparation could not cause the disappearance of spirochetes within twenty-four hours, as in the majority of patients treated with neoarsphenamine. The minimum time required for water-soluble bismuth to act was four days in one and six days in 8 cases. Inasmuch as mercury is greatly inferior to bismuth as a spirillicide, the obvious superiority of even one of the weaker though widely used arsphenamines (neoarsphenamine) is beyond dispute.

Our experience in the evaluation of certain arsenical drugs suggests that the rate of disappearance of spirochetes from the lesions of early syphilis is variable, dependent on many factors: cooperation of the patient, sanchoomness of the examiner, type and condition of the apparatus, reactivity of the patient, and the quality of the drug. Thus, with the same lot of drug the spirochetes may disappear from the lesions of early syphilis in from less than twenty-four hours to more than five days after the administration of a single dose of drug. Size of dose, within the limits studied (0.3 to 0.6 Gm.) apparently has little effect, in our experience, on the rate of disappearance of the spirochetes. On the other hand, Leopold found the rate of disappearance of spirochetes from lesions in patients treated with arsphenamine to be proportionate to the dosage. This was confirmed by Katz, who noted that half the full dose of arsphenamine seemed to be as rapidly spirillicidal as the full dose.

Special Cases—Pentavalent Arsenicals.—Mention of tryparsamide, acetarsone (spirocid, stovarsol), and aldarsone, which are pentavalent arsenicals, should be inserted at this point for fuller discussion later. These drugs, especially tryparsamide and aldarsone, show a relative lack of spirocheticidal action, but have a powerful effect upon syphilis of the nervous system, especially paresis. While it would not be advisable and in fact is impossible to speak of tryparsamide as a spirillicidal arsenical in the sense appropriate to the clinical scheme thus far developed for making clear the action of these drugs, it is, of course, quite conceivable that tryparsamide to

increase following narcosis. Owing to toxic effects, he considered the method unproductive question of some interest in the later discussion of the simultaneous administration of arsenicals with fever therapy. Leonard has confirmed the finding of several other investigators as to the relative impenetrability of brain tissue to bismuth. It should be recalled that tryparsamide is not *spirillicidal to any significant degree. An interesting* by-product of this investigation was the migration of the introduced *Spirochaeta pallida* from the spinal canal to the testicles, in which sit primary lesions developed without local reaction in the nervous system.

In any event, it is apparent, either that the chemical properties of a tissue which make it incapable of combining with certain drugs or the impenetrability of the tissue or its membranes to drugs with differing electrochemical properties (i. e. colloids *versus* crystalloids) will play an important part in future investigations for singling out individual structures for specially effective treatment. Hanzlik and his coworkers (1935 1937 1938) for example, have utilized such considerations in developing a compound of bismuth iodobismitol which it was hoped would be especially effective in penetrating the nervous system. Their claims, however have not been confirmed by Klauder and Brown (1934) Sezary Barbé and Lackenbacher (1934) or by Levaditi and his coworkers (1933)

Drug Fastness and Treatment Resistant Syphilis.—The clinician has become so accustomed to the rapid disappearance of the early manifestation of syphilis under the modern antisyphilitic drugs that any delay is sure to excite concern. In spite of the fact that the concept of drug fastness or the failure of syphilitic lesions to respond normally to the antisyphilitic agents (arsenicals, bismuth salts and mercurials) antedates the clinical use of the modern antisyphilitic remedies, there is still no definite knowledge as to the mechanism and cause of this phenomenon. At the beginning of the arsphenamine era there were relatively few reported cases of treatment resistance. Since 1921 an increasing number of examples of treatment-resistance in syphilis has appeared in the European literature. No such increase has been noted in the United States. (Moore and Robinson 1930 Beerman 1936.)

Treatment-resistance may occur in any phase of syphilis. From the clinical standpoint treatment-resistance in early syphilis consists essentially of (1) persistence of lesions, (2) persistence of positive blood serological tests, and (3) persistence of spirochetes in lesions in spite of usually adequate treatment. Although serologic (reagin) fastness and serologic relapse during therapy are regarded by some as manifestations of treatment-refractory syphilis, the persistence of *Spirochaeta pallida* in the lesions is the most valid criterion of this state in human syphilis. Various grades of clinical resistance to treatment have been described ranging from instances of relative resistance through true resistance to a condition wherein treatment actually seems to stimulate the disease (arsenoactivation). The cutaneous lesions of treatment-resistant syphilis are often papulosquamous and psoriasiform and have a characteristic localization, being distributed as a rule on the face neck, penis and upper extremities. Many treatment-resistant patients react poorly to arsphenamine (Jeanner). Seronegative secondary syphilis ordinarily is rare (about 1 per cent) but in treatment-resistance syphilis the tendency to negative blood serological reactions occurs about five times as often. Moore and Kemp noted that the positive blood serologic reaction of a group of treatment-resistant patients tended to become negative very readily under treatment.

The *consensus* in the literature maintains that the cause of treatment resistant syphilis lies in one factor or in combinations of three factors the

peculiarities of the host, the potency of the drug and the peculiarities of the strain of *Spirochaeta pallida*

The host has been considered by many to play an important, if not the most important, rôle in the causation of treatment-resistant syphilis. Many arguments and observations have been adduced in support of this deduction. Some authors believe that the deprivations of the first world war may have been responsible for the increase of treatment-resistant syphilis in Germany. Others, however, note that treatment-resistant syphilis has increased in countries not affected by the first world war blockade. Some investigators think that the reaction to arsphenamine is influenced by such factors as race, climate, diet, habits, nervous strain, intercurrent disease and bodily constitution. (Moore and Robinson, 1930.) Another group holds that certain individuals lack the ability to change the inactive form of an arsphenamine, as administered, to the "avid" or potent form in the body (Miller 1931). Recently Netherton (1937) has suggested an ingenious method of testing this idea by observing whether or not arsenoxide, the "avid" form of arsphenamine, is effective against arsphenamine-resistant syphilis. Experimental testing of this idea is balked by the fact that Raiziss and Severac (1935) have found that the minimum curative dose of arsenoxide for rabbit syphilis is very nearly the maximum tolerated dose. In a clinical study, however, Beerman, Ingraham and Parner found in common with other observers (Beckh and Kulchar 1930) (Robinson 1937), (Dalton 1937), that syphilis may resist arsenoxide (mapharsen) treatment and that this drug behaves exactly as any other arsenical in regard to treatment-resistant syphilis. Netherton (1937) claimed that resistance to both arsenic and the heavy metals tended to incriminate the host as responsible for the condition. In addition, a number of vague but imposing theories involving the host have been advanced as possible explanations of treatment-resistant syphilis. They include such items as changes of the drug within the body into a form to which the parasite is immune (a variant of the metabolism theory noted above) and failure of the defensive powers of the host. The latter may be resident in certain cells or may result if all the tissues of the host become "immune" to the injected medicament. Several authors, most recently Netherton (1937) have argued that different responses to treatment in partners of conjugal syphilis means that with the same strain of *Spirochaeta pallida* under similar conditions the progress of treatment becomes a function of host variation. This argument would hold were it not for the fact that certain observers have seen conjugal syphilis evolve with remarkable synchronization. Finally a miscellaneous collection of proposals has been advocated with so little sustaining evidence that the limitations of space preclude their enumeration.

Changes and fluctuations in the manufacture of antisyphilitic arsenicals have caused the rôle of these drugs in production of treatment-resistant syphilis to be variously interpreted. No one has succeeded in establishing the drug as the basic factor in treatment-resistance, but some facts merit further consideration. For instance: the potency of arsenicals has been diminished by efforts to reduce reactions to them; the consequences of this change are highly debatable. Various manufacturers also have produced drugs of varied efficiency, the variations being caused either by ineffectiveness of a given formula, or by lack of uniformity in the processing of similar formulae. Even drugs of different lots, presumably made under identical conditions and by identical methods, display variable curative properties. Finally it is possible that an effective drug may induce treatment-resistance when it is used in subcurative doses; for example, the recent report by Beckh and Kulchar (1939) of eighteen cases of syphilis resistant to various arsenicals, including mapharsen, in which more cases occurred after combined (concurrent, simultaneous) than after an alternative plan of treatment, may have been due to chronic underdosage of each component to avoid reactions.

The part which *Spirochaeta pallida* may play in causing treatment-resistance has received much attention. Several authorities have suggested that this organism itself may be directly or indirectly responsible for ineffective treatment. Some have suggested that the spirochetes may be located where treatment is ineffectual, e. g. in the brain, or that varied phases in the life cycle determine different reactions to drugs. Indirect evidence of the possible rôle of *Spirochaeta pallida* consists largely of clinical observations which suggest treatment-resistant strains. Similarity in the course of some cases of conjugal syphilis suggests that strains may differ in their qualities. This argument, however, is no more convincing than that which is supposed to establish the host's causative rôle in treatment-resistance. Laboratory investigation, in our opinion, affords the most indubitable evidence of the importance of *Spirochaeta pallida* in the causation of treatment-resistance, and incidentally suggests the possible occurrence of drug-fast strains.

Evidence of the existence of drug-fast strains is based upon (1) studies of the effects of drugs upon spirochetes *in vitro*, (2) attempts to increase the tolerance of spirochetes to larger doses of drugs by subjecting infected animals to subtherapeutic doses; and, finally (3) attempts to rear in animals strains of spirochetes obtained from patients known to be resistant to treat-

ment Before presenting the data relative t these methods of laboratory study one must concede the basic possibility of the existence of strains of this organism ith individual biologic and elective localization characteristics. While evidence on this point is conflicting, there is slight balance in favor of the independent existence of strains in the biologic sense.

Akatsu and Noguchi in 1917 found that *Spirochaeta pallida* could be made five and half times more resistant t increasing doses of drugs by cultivating the organisms in media containing various arsenicals and mercuric chloride in concentrations just short of suppressing the growth completely Stjoskal and Fantl, studying the viability of *Spirochaeta pallida* in the hanging drop, concluded that arsphenamine kills spirochetes from mercury-treated patients much more slowly than it does those from untreated patients. Rubin and Szentkiralyi' studies did not, however confirm this observation that preliminary use of mercury increases the resistance t subsequent arsenical treatment. Study of the arsenic content of spirochetes may throw some light upon the question of the spirochetal factor in treatment-resistance. Feldt, in his study of the metal content of the spirochetes of relapsing fever after treatment of rats infected with an arsphenamine-fast strain, noted that arsphenamine-fast strains take up as much arsenic as normal strains, in con trast t trypanosomes in which resistant strains take up less arsenic tha normal strains. As yet no studies have ppeared on the comparative arsenic absorptive capacity of arsphenamine-fast and ordinary *Spirochaeta pallida*.

In 1910 Margulies studied the effect of subcurative doses of arsphenamine on trypanosomes in mice and on spirochetes, including *Spirochaeta pallida*, in rabbits. She found that the spirochetes, in contrast t the trypanosomes, failed t become accustomed to small doses of arsphenamine Nichols and Rothermundt and Dale likewise failed to demonstrat arsenic-fast properties of *Spirochaeta pallida* in experimental rabbit syphilis. Launoy and Levaditi (1912) were able to produce mercury fastness of *Spirochaeta pallida* in rabbits by the use of subcurative doses of mercury Frei, however was unable to confirm their findings. Gonder (1912) using subtherapeutic doses, produced the first artificial arsenical fastness of spirochetes in animal (*Spirochaeta gallinarum* and *Spirochaeta recurrentis*) He suggested such possibility for *Spirochaeta pallida*. Klauder (1924) by administration of subcurative doses of arsphenamine, as ble t develop strain of spirochetes in which the therapeutically effective dose of arsphenamine was raised 68.0 per cent, showing actual resistance of the infecting organism t the arsenical. These arsphenamine-resistant spirochetes ere normally sensitive to bismuth. Feldt has recently confirmed this ork. On the other hand, Greenbaum and Rule (1936) reported that they had used Klauder strain of *Spirochaeta pallida* and his technique during three years experimentation, but that repeated exposure to small doses of arsphenamine did not produce increased resistance. Sei and Giemsa were unable to produce bismuth fastness in *Spirochaeta pallida* by treating syphilitic rabbits with gradually increasing subtherapeutic doses of bismuth.

In summary w may say that few early experimental studies (Margulies, Nichols, Rothermundt and Dale Frei) seemed to indicate that treatment-resistance could not be induced experimentally by subtherapeutic doses of drugs. Other early studies and most recent ones, however suggest that resistance to drugs, or progression of the disease in spite of treatment, can be produced by experimentally exposing *Spirochaeta pallida* to inadequate doses. Recent extensive experience of the Cooperative Clinical Group also seems to show that small doses induce tr t ment-resistance. (Stokes, Usilton and coworkers, 1934)

Many investigators (Hoffmann and Armuzzi, Navarro-Martin, Jesner Nothaas, Bismosero, Zoon, Schoch and Stern, Schoch) have inoculated animals ith organisms from treatment resistant patients in ttempts to determine whether resistance depends upon altered biological properties of *Spirochaeta pallida*. All except Schoch (1937) and Beerman agree with Kolle observation, made in 1924, that strains of *Spirochaeta pallida* isolated from treatment-resistant human beings apparently were not treatment-resistant in rabbits. The investigations of those who feel that spirochetes from treatment-resistant patients lose their resistance in rabbits, how ever are open t several criticisms. In the first place, most of the studies were of short duration Furthermore, the criteria of treatment-resistance in rabbits used in most of these experiments (disappearance of spirochetes and lesions) are not reliable. A more significant index of sterilization is the popliteal lymph node transfer method of Brown and Pearce which was employed in the study of Beerman (1936, 1938) and Beerman and Severac (1942) Another possible cause of failure is that the organisms may lose their treatment-resistance when transferred from man t rabbit.

In 1932 Beerman obtained strain of *Spirochaeta pallida* from patient whose infection had been uninfluenced by total of 5.4 Gm. of various arsenicals. In summary study of this strain to date (1942) Beerman and Severac showed that over nine and half years 13 of 51 rabbits infected with this strain ere not cured by doses of potent arsphenamine ranging from slightly more to almost twice the curative dose for rabbit syphilis required by the Nichols-Hough strain

of *Spirochaeta pallida*. Chains of treatment refractoriness noted by Beerman and Severac suggested a possible explanation for the unpredictable way in which treatment-resistance affects one or both parties in conjugal syphilis presumably caused by the same strain of *Spirochaeta pallida*.

The prevention of treatment resistant syphilis depends largely upon adequate treatment of early syphilis This includes careful and frequent examination of the relapse sites abandonment of the old idea of abortive cure high initial dosage of the arsenical alternating treatment use of more effective preparations (arsphenamine in preference to neoarsphenamine) improvement in the health and hygiene of the patient.

Fully established treatment-resistance in syphilis may respond to (1) changing the preparation or drug used to another member of the same group e.g from neoarsphenamine to arsphenamine (606) (2) changing the manufacturer's brand of the same drug (3) changing to another type of antisyphilitic agent e g from arsenicals to bismuth salts mercurials or minor antisyphilitic drugs, especially gold Among nonspecific measures are included (1) high caloric diet (2) temporary suspension of antisyphilitic treatment (3) elimination of other intercurrent systemic diseases (4) shock therapy with milk, gonococcus vaccine, autohemotherapy sodium nucleinate fever induced by malaria or other methods

An excellent example of the parasitological criterion of persistence of spirochetes is furnished by the case reported by T H. Miller in which a three-day old primary lesion, darkfield positive and seronegative to Kolmer and Kahn tests continued to develop in size and the serological tests to become slightly and then strongly positive during a period of thirty-eight days in which the patient received 7 injections of arsphenamine (606) with the continued presence of *Spirochaeta pallida* in the primary lesion and the obtaining of a positive gland aspiration. The arsphenamine employed was from a reliable manufacturer was from two entirely different lots and was shown by subsequent investigation both by the manufacturer and the Public Health Service, to have a trypanocidal activity somewhat higher than that required by the Government standards. The primary lesion healed promptly and the serological tests became negative following two injections of sulpharsphenamine intramuscularly after which treatment was continued with bismuth and sulpharsphenamine The peculiarities of the host in this case were reinforced by a marked tendency to vascular reaction evidenced by repeated nitritoid crises, and the patient ultimately died suddenly of aleukemia hemorrhagica following a sulpharsphenamine injection. A inoculated rabbit unfortunately died and the strain was lost.

It is obvious that in interpreting the clinical phenomenon of drug resistance especially to arsphenamine, the therapeutic efficacy of the drug as such must be carefully proved. It seems not improbable that outbursts of arsenic-fastness in the syphilitic population of individual localities such as that of Lyons, as reported by Nicolas may be due to the therapeutic inefficiency of a widely distributed lot or brand of such a drug as neoarsphenamine which is known to fluctuate markedly in its therapeutic potency

Treatment Allergy —The arsphenamines have a distinctive and unfortunate peculiarity of great importance to the general management of treatment for syphilis This is the ability when insufficiently used particularly to induce a state of hypersusceptibility in the patient which results in fulminating relapse, provided the infection has not been extinguished The analogy of this peculiar state to the "umstimmung" or allergy of late syphilis is quite apparent clinically for the allergic type of relapse usually takes on the clinical characteristic of huge and destructive gumma formation in skin bones, or even the nervous system A convenient though by no means an evaluated theory of this sometimes disastrous result of insufficient treatment is the

view that the rapid destruction of the organisms of the disease by the arsphenamine group of drugs deprives the body of its one primordial and essential stimulus to fight the infection on its own account, namely the presence over a long period of time of the pathogenic agent. It is essential therefore, to impress both patient and physician especially in the case of an early infection with the understanding that curative treatment is something of an all-or-none affair If not followed through to a finish the patient is left both without cure and without defence. In the older mercurial days, he was left without cure but with some though an imperfect defence Correspondingly the physician who unwisely adheres to short arsphenamine courses unsupported by other methods of treatment is criticizable in that he has laid his patient open to the possibilities of treatment allergy The relation between treatment allergy and arsenic-fastness may be closer than would be imagined at first thought in that the persistent positive blood serologic reaction, for example may represent a phase of serological hypersusceptibility to a very small number of organisms of little practical importance to the future of the patient. Speculation aside however it cannot be too strongly emphasized that much of the blame that has been laid at the door of the arsphenamines for the induction of premature neurosyphilis resistant, destructive lesions, and inveterate relapse or serological fastness is the result of the *abuse* not the proper *use* of the drug. Too little arsphenamine especially in the early case, is at times more dangerous than too much or none at all (see Figs 423 and 434) It is always necessary to carry the drug to a more or less empirical maximum and essential, moreover for reasons presently to be considered, to reinforce its action with that of a heavy metal. Cases of malignant precocious tertiarism in spite of intensive arsphenamine therapy have been reported by Pinard Vernier and Vernini, Fruehl and others

NONSPECIFIC THERAPY IN SYPHILIS

General influences of a nonspecific character affecting the course and therefore the treatment of syphilis have been mentioned as follows influence of sunlight and thyroid activity in experimental animals influence of climate race, privation and of stress and strain just cited in connection with arsphenamine resistance the deleterious effects of focal and intercurrent infections trauma and other influences creating a *locus minoris resistentiae* protective effect of extensive involvement of the skin and osseous structures particularly both in experimental animals and in man effect of the general reaction of the disease in the secondary stage as a preventive of relapse.

An interesting recent therapeutic development, combining, in all probability the action of light, the stimulation of the skin to inflammatory reaction, and possible nonspecific protein effect is the combination of quartz lamp therapy and autohemotherapy (whole blood injections) recently reported on by Rajka and Radnai as particularly successful in the nonspecific treatment of tabes. W have personally employed ultraviolet light for some years in the relief of tabetic lightning pains.

Chemotherapeutic Effects with Nonspecific Phases—Nonspecific Uses of Mercury—While mercury is probably the most specific drug in its action in the entire group of antisyphilitic medicaments, its beneficial effects in lichen planus, nonspecific periostitis, in nonsyphilitic uveitis and chorioiditis, lupus vulgaris and even in epidemic influenza, are well known

Nonspecific Effects of Bismuth.—These are being increasingly discovered

Lupus erythematosus has been treated effectively with bismuth by Nicolas and his co-workers (1929) and MacKenna. We believe that the hydroxide is especially useful. We have also observed good effects in lichen planus (*cf* Grossman, 1932, Sonck, 1936)

Lurie 1932, showed that palmar and plantar verrucae respond to intramuscular injection of bismuth salicylate Shellow (1931) modified the treatment by using a soluble bismuth preparation locally (The response of verrucae to suggestion (Bloch) must be recalled in evaluation of any therapeutic procedure) Recently Schwartz (1939) suggested the use of bismuth injections to control the course of therapeutic malaria (Cole DeOreo, Driver Johnson and Schwartz, 1940) This observation was confirmed by Brunsting and Love (1940) and Young *et al.* (1943) Mais ld (1940) treated tonsillitis with bismuth and Saltzman (1942) found it effective in two cases of infectious mononucleosis. It is also useful in treating morphea. An interesting side action of bismuth is the possibility that latent plumbism may become active after the injection of it as an antisyphilitic agent (T Epstein, 1940).

Nonspecific Effects of the Arsphenamines.—A part of the striking and numerous nonspecific effects of the arsphenamines arise undoubtedly from the contained arsenic. Thus the tonic action of the arsphenamines as contrasted with the depressant influence of the mercurials if not a major is at least a most welcome addition to modern treatment regimens for syphilis.

The anemias and hospital pallors, falling weight curves and intractable anorexias are now part of the syphilological limbo of the almost-forgotten mercurial days. In fact the patient receiving an arsphenamine is today in more danger of seeming too well than too ill and thus easily discounts his plight and imagines himself the victim of a trivial ailment. The combined tonic and healing effects, the latter of course in part but not altogether specific of an arsphenamine give this group of drugs an unrivalled therapeutic "push" or curative power Where the older treatment slowly and laboriously educated reluctant body cells to defend themselves, the newer medication sweeps upon the field with a dash which for the first time in history seems to make almost visible the promise of actual extinction of all the organisms. Whether cure is possible or not, there is no mistaking the immense contribution in power and effectiveness brought into the syphilotherapeutic armament by the arsphenamines.

The extent and range of the action of the arsphenamines upon disease processes other than syphilis are strikingly indicated in Fig 57 which endeavors to catalogue under four grades of therapeutic utility the large number of conditions in which these drugs have been found useful The nonspecific aspects of the mechanism were presented on page 140 in connection with the modus operandi of the drugs

A part of the action in certain of the conditions enumerated arises from the stimulation of defence and the formation of agglutinins, lysins and antibodies of low specificity in part, perhaps, not only through action on the reticulo-endothelial system but through parasiticidal and bactericidal action in the intestines and the ill-defined tonic effect of arsenic. Nicolas, Gourmont, Gaté and Charlet showed that the administration of small doses of arsphenamine produced definite increase in agglutinins for tubercle bacilli in the blood of patients with tuberculosis. Toyama and Kolmer showed that large doses of either mercury or arsphenamine inhibited the formation of agglutinins and lysins, while small doses encouraged their formation. Tzanck and Pelsois, and Ravaut, in France, and Stokes in this country called attention to the clinical results which could be secured by treating tuberculids and tuberculous lymph nodes with the arsphenamines, effects sometimes quite as striking as those obtained in syphilis and a potentially fertile source of error in diagnosis. In conjunction with these observations, Benedict and Stokes have noted improvement in patients with inflammations of the uveal tract which could not be traced to syphilis, and Benedict and O'Leary published a report of results in a series of patients in most of whom syphilis had been quite definitely excluded The arsphenamines have also been successfully employed in some cases of blastomycosis (the late F G Harris rated it as almost specific in this condition), actinomycosis, and sporotrichosis, in multiple benign sarcoids, Hodgkin disease, lymphosarcoma, and mycosis fungoides in streptococcus septicemia; in Vincent's angina and erythema multiforme in intestinal infections with Lamblia and Entamoeba histolytica; in trichiniasis, malaria and pellagra and in multiple sclerosis in the absence of syphilis. Osgood and

his associates (1938–1942) demonstrated the superior effectiveness of neoarsphenamine over various members of the sulfonamide group by the ingenious device of the marrow culture technic hich permits controlled study of therapeutic agents against bacterial infections in the presence of human cells. By this method it was show that neoarsphenamine in concentration of three parts in a million was more effective against *Staphylococcu* *reu* or *Streptococcus viridans* than one t 10,000 concentration of either sulfanilamide or sulfapyridine nd did not significantly damage marrow cells. (1939–40)

Fig. 47

THERAPEUTIC USEFULNESS OF TRIVALENT ARSENICALS IN DISEASES OTHER THAN SYPHILIS

Distinctiv value	Acceptable	Occasional or variable	Debatable (isolated reports)
Bejel.	Amebiasis.	Actinomycosis.	Adenitis.
Pinta.	Arthritis (chronic)	Anemia pernicious (nonsyphilitic)	Agranulocytic angina.
Pneumonia (complicating syphilis)	Blastomycosis.	Anthrax.	Erysipelas.
Pulmonary spirochetosis.	Chorioiditis.	Aphthous stomatitis.	Leprosy
Rat-b t fever	Erythema multiforme.	Echinococcus infection	Liche planus.
Relapsing fever	Erythema nodosum	Glanders.	Lymph g loma venereum.
Rocky mountain spotted fever	Lamblia infections.	Gonorrhea.	Typhoid fever
Septic scarlet fever	Lupu erythematosus	Herpes zoster	Undulant fever
Y	Multiple sclerosis	Hodgkin disease	V ricella.
	Tuberculosis.	Leukemia.	Yellow fever
	Adenitis.	Lymphosarcoma	
	Lupus vulgaris.	Malaria, black water fever	
	Erythema induratum.	Mycosis fungoides	
	Sarcoid.	Pellagra.	
	Synovitis.	Pemphigus.	
	Tuberculid.	Periadenitis mucosa.	
	Uveitis.	Periostitis (nonspecific)	
	Vincent angina	Puerperal fever	
		Pyelitis	
		Septicemia (streptococcal)	
		Trichiniasis.	
		Verruca plana.	

Of these varied uses, the application of treatment for syphilis in tuberculids, tuberculosis n the sarcoids, n nonspecific periostitis and osteitis in amebiasis and mycoses and in multiple sclerosis in the absence of syphilis, has led to confusion with syphilis. This point will be reemphasized in the discussion of the technic of therapeutic tests. The investigation for syphilis in all cases in which an arsphenamine is to be used for nonspecific action, should be thorough and yield negative results before treatment is instituted

Nicolas and his collaborators showed that the response to arsphenamine in tuberculosis depended to a considerable extent on whether the patient was showing a good resi tance and was on the upgrade or whether he wa on the

decline If the latter the tuberculosis was more likely to be unfavorably than favorably affected thus we have found to hold true in general for the utilization of nonspecific effects whenever they depend on stimulation of a resistance



Fig 59.—A papulonecrotic tuberculid with ulcerative lesions of erythema induratum and scarring (right leg) suggestive of syphilid There were numerous papulonecrotic lesions, and the history was typical. Full and repeated study for syphilis was negative. The linear scarring of the left leg represents the effort of a surgeon to remove the lesions as varicose ulcers. The patient was later sued for divorce on the ground that because her lesions had cleared up temporarily under arsphenamine she must have syphilitic infection.



Fig. 60.—Sporotrichosis of the thigh (cultural identification) healed by arsphenamine and mercury succinimide without iodides or roentgen-ray

mechanism The best results cannot be expected from patients who are on the downgrade. Where a merely antiparasitic action is invoked as in intestinal parasitism, this consideration is not important.

Uncertainties of Nonspecific Effect.—The securing of nonspecific effect is not a matter of absolute uniformity and it is difficult to analyze the effect of the procedure into its components.



Fig. 60.—Sarcoid infiltration of the face of the subcutaneous or Darier Roussy type.



Fig. 61.—Effect of [illegible] arsphenamine injections on the Darier Roussy sarcoid shown in Fig. 60. Note the large amount necessary to produce this result.



Fig. 62.—Effect of 15 arsphenamine injections on the sarcoid shown in Fig. 60.

In tuberculids the action is fairly constant and improvement takes place at a uniform rate, suggesting the action of treatment in syphilis, though somewhat slower. In tuberculous processes in the glands, throat and skin in the order named, there is less assurance of good effect. In mul-

tiple fibrosis, periostitis and osteitis the effect is secured occasionally but not frequently. In uveitis the results secured depend upon the age of the process, being very good in early acute cases and relatively poor in patients who exhibit old opacities, deposits and scars. The healing of tuberculids and erythema induratum (Chapter XV) is accomplished in from six to eight weeks and in more than 50 per cent is apparently permanent even in this notoriously relapsing condition. Tuberculous glands are occasionally spectacular in response. Sarcoids may require treatment for two or three courses before much effect is apparent, the action probably being due to arsenic which is known to influence these lesions favorably. Flare-ups or therapeutic shocks in tuberculous processes and uveitis occur and may create an even more confusing impression of syphilis. Patients with uveitis should be warned that they may have a flare-up, or they may become alarmed by a temporary decline in vision. The ultimate effect is usually good. If the process is very acute a two-week mercury succinimide preparation is desirable. The repetition of courses in nonspecific therapy does not follow the time-rules of syphilis. Tuberculids usually recur in spring and fall and for this reason and because there seems to be some advantage from a high total arsenic intake three or even four courses are sometimes desirable. Even though patients do not completely escape a recurrence the attacks are much milder and usually free from the constitutional accompaniments of arthralgia, tenosynovitis and anemia that are common in patients who have tuberculids. In other types of cases two courses may be given and further treatment made to depend on symptomatic indications. Focal infections should be removed, if accessible, but their removal is not essential to the securing of a good, though less permanent, therapeutic effect.

NONSPECIFIC PROTEIN AND FEVER THERAPY

The influence of intercurrent febrile infections in causing the involution or amelioration of other primary conditions has long been known. Finger

Fig 63.

CLASSIFICATION OF METHODS OF NONSPECIFIC (FEVER) THERAPY

Physical.	Chemical.	Nonbacterial protein.	Bacterial protein.	Active infection induction.
Diathermy High frequency oscillation. Hot baths. Heated air 1 luminous heat cabinet. 2. air conditioned cabinet (hypertherm) Blankets 1 plain. 2. electrically heated.	Sulfur in oil intramuscularly	Whole milk. Aolan (casein, etc.) Lipoprotein or gan extracts. Yeast extracts.	Typhoid paratyphoid vaccine Typhoid divided dose with H antigen (flagellar) Triple typhoid vaccine by continuous intravenous infusion (?) Pyrifer Coley serum Tuberculin.	Malaria. 1 tertian. 2. quartan. 3. spp. Recurrent fever Rat-bite fever

Lang, and others observed it in connection with various aspects of syphilis and Neumann reported the involution of a macular syphilid under the influence of an intercurrent pneumonia. Buschke and Freymann early observed that febrile arsphenamine eruptions associated with treatment had a particularly beneficial effect on the subsequent course of the syphilitic infection. The spectacular change in the prognosis of general paresis brought about by Wagner von Jauregg's introduction of malarial therapy has probably been chiefly instrumental in focusing attention, heretofore directed for more than

a decade upon chemotherapy upon the new possibilities and problems of nonspecific stimulation of the defence mechanism in syphilis "Stimulation therapy" as Schumacher calls it, can be accompli hed by a variety of methods which are classified in Fig 63

Regardless of the agent employed the first point for the practitioner to appreciate in his employment of nonspecific treatment in syphilis is the one limitation inseparable from the method. It is not appropriate to any treatment regimen which requires the rapid destruction of the *Spirochaeta pallida* In

Fig. 61

THE PHYSIOLOGIC EFFECTS OF NONSPECIFIC PROTEIN AND FEVER THERAPY
(A Summary Based on Nonnenbruch, Miller Jaffe, Krusen and Elkins, Solomon and Kopp, Simpson and Others)

1 A cellular rather than humoral therapy
2. Colloidal "shake-up" changes in tissue structure
3 Local inflammatory reaction aroused t disease sit
4 Products of increased cell break-down ppear in the blood
( ) adrenalin-like substances, (b) digitalis-like substances ( ) substances affecting the theoretical "heat-center —Freund.
5. W ter balance changes.
6. Blood changes acidosis followed by alkalosis sodium chloride prevents loss of base nd chloride (Danielson nd Stecher 1935)
7 Vascular permeability altered. Shock syndrome (Kopp and Solomon, 1937)
8. Increase in proteolytic nd lipoproteolytic enzymes (Jobling and Peterson, Schumacher)
9 Leukopenia followed by leukocytosis (macrophagocytosis) (Doa and Hargraves, 1936 1938)
10 Stimulation and hyperplasia of the reticulo-endothelial system (macrophagocytosis, etc.)
11 Increased nitrogen output.
12. Mineral metabolism influenced. Loss of sodium chloride
13. Anaphylactic shock effects.
14 Desensitization against proteins. Rise in resistance in general (Rusznyak and Koranyi) Inhibition of classical anaphylaxis in the guinea-pig (DeKruif and Simpson, 1940)
15 Antibody formation nd mobilization associated with, and increased by rise in temperature
16 Effects on sympathetic nervous system (blood pressure, increase in pulse rate, increase in pulse pressure increase in blood flow decrease in blood volume (G bson and Kopp, 1936 S. L. Osborne, 1941) rise in metabolic rate, deeper respiration ith little effect on rat inability of postural vasomotor reflex to react normally (Kopp, 1935–1939)
17 At fever levels the tolerated dose of an arsenical decreases (Mapharsen in experimental animals), but the therapeutic effectiveness of the drug increases far more rapidly (Carpenter and Warren)
18. Destruction of micro-organisms b body temperatures equalling their thermal death point.

THE *MODUS OPERANDI* REMAINS UNEXPLAINED

spite of experimental data strongly indicating that high body temperatures are spirochetacidal (Carpenter Boak and associates, 1930–1942, Bessemans and associates, 1929–1933) or that high temperatures increase the effectiveness of an injected drug (mapharsen) clinical experience shows that short periods of fever or a single prolonged fever are inadequate for the treatment of early syphilis. (Epstein and Cohen, 1935 Neumann, Lawless and Osborne 1936, Simpson and Kendell 1937 Simpson, Kendell, Rose 1942, Boak, Carpenter and associates, 1934 1942) Hence it should not be used without adjunct chemotherapy in the treatment of early infectious syphilis, a principle which

even the most enthusiastic malarial therapists such as Kyrle for example have not felt willing to set aside. Nonspecific therapy will unquestionably achieve by one or another means, combined with chemotherapy for example Kyrle (1924) Simpson, Kendell and Rose (1942) Boak, Carpenter and Warren (1942) a routine place in the treatment both of early resistant and late syphilis, but certainly in the present state of knowledge a vigorous warning which can be easily reinforced by a study of the literature should be given against any attempt to substitute nonspecific therapy for the use of powerful spirillicidal drugs, such as the arsphenamines, in the public health control of the disease

The *Modus Operandi* of Nonspecific Therapy —Some of the differences in viewpoint and method which beset present-day practice and theory in nonspecific therapy are we believe due to a lack of appreciation of the extraordinary range of action involved in this form of treatment. In order to illustrate the extreme complexity of the problem and the impossibility of admitting any one mode of action to be the sole effective one we have drawn up Fig 64 based upon the admirable recent summaries of Nonnenbruch, Miller Jaffe Krusen and Elkins Solomon and Kopp Simpson and others From this table it will appear that here are at least eighteen different processes going forward at practically one and the same time in the patient who is receiving any one of the various forms of nonspecific protein or "fever therapy

The chief effective modes of action re in all probability the stimulation and hyperplasia of the reticulo-endothelial system which follows all bacterial and foreign-protein invasion; the increase in proteolytic and lipoproteolytic enzymes, the latter emphasized by Schumacher as the principal feature of the nonspecific defence against syphilis, antibody formation and mobilization associated with, and increased by the rise in temperature; and the local inflammatory reaction aroused t disease sites by these forms of treatment The function of the anaphylactic mechanism, of the metabolic changes, of the leukopenia followed by leukocytosis and of colloidal shake-up of the body cells is all uncertainly defined It is not ithout reason, therefore, that Nonnenbruch concludes his summary by saying that the *modus operandi* in nonspecific therapy remains unexplained. The wide range of theories is well illustrated by the discussions of Gerstmann and of Peruts. Schumacher has repeatedly stressed the lipoproteolytic mechanism and has built up an elaborat and very plausible theory round this particular element, supporting it by such observations as those of Levaditi on the increased effect of bismuth in lipoprotein suspension and similar effects claimed for the arsphenamines (yeast protein injection) The large share taken by the reticulo-endothelial mechanism is summarized by Jaff in its general pplication. Histologic studies show that foreign proteins are productive of swelling, proliferation, basophilic staining and vacuole formation within the Kupffer cells. Macrophagocytosis by reticulo-endothelial cells certainly far outranks ordinary leukocytic phagocytosis in the control of many infections, and this is probably especially true of syphilis. The claimed superiority of the introduction of living infectious agent, such as the malarial parasite, in bringing about these changes in the reticulo-endothelial defences is the basis of the inference that spirochetes incidentally present are probably phagocytised in the same manner though this can hardly be said as yet to have been demonstrated. The only direct studies of resistance to spirochetes thus far recorded are those of Pentschew of Levaditi and of Deutz, in which it appears that the *Spirochaeta gallinarum* injected into the blood of young rabbits or mice, ppears for short time nd then disappears, unless the reticulo-endothelium system has been blocked, in which case the spirochetosis of the blood of the mouse is markedly increased.

The instrumentality of rise of temperature of the body tissues as such in the destruction of the *Spirochaeta pallida* has recently been emphasized by Schamberg and Rule who observed that rabbits could be protected from syphilis after intratesticular inoculation of *Spirochaeta pallida* if they received eleven consecutive daily hot baths under certain conditions which would produce an average rise of temperature of 4 F Believing that the thermal death point of the *Spirochaeta pallida* could be reached within the limits of temperature endurance of the host, they subjected rabbits t series of hot baths and found that the primary lesion healed almost with the rapidity of arsphenamine therapy and more quickly than after injections of bismuth. The

organisms disappeared in less than eight days and the testicles were entirely normal in seventeen days. The organisms were still present after forty-eight hours so that even under the favorable conditions of animal experiment the method does not equal the use of good arsphenamine or mapharsen in the rate of spirochete destruction.

The importance of adequate temperature rises and their relation to the thermal death point of *Spirochaeta pallida* is most effectively discussed in terms of the latest investigation in Simpson, Kendell and Rose review of artificial fever combined with chemotherapy in Supplement 16, Venereal Disease Information. Bessemans and his associates found that the application of heat to the testicular syphilomas of rabbits, regardless of the method used, destroyed *Spirochaeta pallida* when the temperature in the syphilitic lesion (as measured by small thermocouples) was maintained for one hour at 106° Fahrenheit (42° Centigrade) or for two hours at 104 Fahrenheit (40° Centigrade). Bessemans also found that *Spirochaeta pallida* in the popliteal nodes of the syphilitic rabbit rarely lose their virulence if the rabbit is subjected to sufficiently high body temperature only to destroy the spirochetes in the external lesions. It sometimes required a temperature of 114.8° Fahrenheit (46° Centigrade) for one hour to achieve the same results. On the other hand Carpenter and coworkers found that a body temperature of 106.7-107.6 Fahrenheit (41.5-42 Centigrade) maintained for six hours was uniformly sufficient to destroy *Spirochaeta pallida* both in the testicles and in the popliteal lymph nodes of syphilitic rabbits. This has been confirmed by Simpson and coworkers. Thus the in vivo thermal death time of *Spirochaeta pallida* will vary both with the height and the duration of temperature. The subsequent work of Bessemans, interrupted by the invasion of Belgium, and the now more complete experimental studies of Boak, Carpenter and Warren, appear to have clearly indicated that subcurative doses of an effective arsenical, combined with a subcurative elevation of body temperature give superior results in the treatment of experimental syphilis to the administration of larger amounts of drugs or higher temperatures alone.

Nonspecific Therapy in Early and Latent Syphilis.—Applying other methods than the induction of infection to the use of nonspecific therapy in early syphilis, Greenbaum and Wright showed that 4 per cent suspension of milk protein produced the involution of a certain proportion of secondary lesions and later that milk injections used in conjunction with neoarsphenamine were more effective in reversing the blood Wassermann reaction than neoarsphenamine used alone. They emphasize however that where any effort is made to apply such nonspecific therapy combinations to the treatment of early syphilis, the spirillicidal drugs should be used first because of the necessity for a rapid reduction of organisms. The distinction of having thoroughly studied the possibilities of malarial therapy in the treatment of early syphilis belongs to the late Kyrle who, by a large series of cases whose evaluation was interrupted by his death, succeeded in showing that in the early stages at least the treatment had not proved itself but that malarial courses, when administered between courses of the arsphenamines, produced a marked beneficial effect on the general course of the infection. Von Berde pointed out that while the primary lesion healed after the malarial siege, the adenitis and eruption subsequently developed, so that the method should be strictly interdicted in the treatment of seronegative primary syphilis (*vide supra*). Once the secondary eruption had, however, developed, the response was much more satisfactory. Instances were observed in which the malarial therapy gave rise to an induced allergic type of reaction, making the infection worse and leading to severe and destructive lesions. The use of fever induced by typhoid vaccine, in combination with chemotherapy has greatly impressed us as a method of dealing with resistant recurrences in late syphilis—particularly nodular infiltrative cutaneous lesions and bone lesions. The weekly induction of a bout of fever (two to four hours above 104° F.) with an injection of a moderate dose of any one of the standard arsenicals (by weight) causes involution of lesions previously resistant to arsenical and combined heavy metal therapy. Relapses may occur after a single or even two eight-treatment courses, but persistence has thus far yielded satisfactory results.

The combination of alternating courses of fever therapy and chemotherapy or the initiation of treatment with fever therapy particularly malaria in the case of interstitial keratitis as a complication of congenital syphilis, has now become established in this country at least, as standard procedure following the recommendations of Klauder and coworkers, representing the Cooperative Clinical Group. Practically the same statement may be made of the obstinate and destructive syphilomas of bone encountered in congenital syphilis, and of course of congenital syphilitic lesions of the nervous system, especially paresis.

Evidence is rapidly accumulating to indicate that combined fever and chemotherapy when facilities and experience for their proper use are available is one of the most effective methods of attack upon any phase of a syphilitic infection in which positive contraindications do not exist. The steady improvement in physical methods of inducing fever their simplification, and the apparently increased effectiveness of the arsenicals without corresponding increase in toxicity

have outdated the argument as t the advisability of the routine induction of malaria as part of the treatment of early syphilis. Other less objectionable method are rapidly becoming vailable. Kyrle and his successor Kerl, and Zieler while in the main proponent of the use of malaria in many phases of the treatment of syphilis, have influenced opinion more and more towards the extensive but not necessarily routine use of fever in the general treatment of syphilis. Zieler in summarizing the literature defined the limitations of effectiveness in certain specific states and syphilitic involvements, and insisted on thorough-going nd vigorous treatment with the arsenicals and heavy metals.

Combined Fever and Chemotherapy in Early Syphilis.—This subject will be more specifically reviewed under the treatment of early syphilis, but the most extended experience to date—that of Simpson Kendell and Rose (*loc cit.*)—summarizes the principles. In control series since 1032 these authors believe they have shown that fever alone or chemotherapy alone (the latter however not conforming to the full standard system for the chemotherapeutic treatment of early syphilis) was insufficient to produce satisfactory results. A combination of the two however in seventy-seven patients, of whom sixty have been quite carefully followed, indicates that in seronegative primary cases, the serologic reactions never become positive. Involution of lesions and disappearance of spirochetes progress at a normal rate. In seropositive primary syphilis, 02 per cent achieved satisfactory results in a single course of combined treatment which included a total of fifty hours with fever at an average temperature of 105.8° F (ten weekly sessions of five hours each) and later shorter courses aggregating thirty-six hours at the same fever were combined with chemotherapy which while not exactly defined apparently approximated thirty concurrent injections of arsenical and bismuth compounds. The two relapsing cases in this series achieved serologic negativity following a second course of fever-chemotherapy Two out of twenty patients with secondary manifestations in the first year of the disease (10 per cent) failed to achieve serologic negativity in eight cases of later and more resistant types the responses were less satisfactory and repeated courses more often necessary One of the interesting effects of this type of treatment was apparently the absence of exfoliative skin reaction which can conceivably be interpreted as an evidence of the antiallergic or desensitizing effect of the fever phase of the treatment. The combination of intensified short-term chemotherapy with fever is in process of trial by these workers and others (Thomas and Wexler 1941, Kaplan, 1042)

Physical Methods.—The trend in the use of physical methods of induction of fever in the treatment of syphilis has been first towards an increasing demonstration of the importance of the maintenance of high temperature for relatively long periods—and second the importance and feasibility of a steady simplification of technic. It is now apparent that the electrical methods of inducing fever by the oscillating current and by diathermy are unnecessary have no distinctive merit, and do have some dangers, including particularly the induction of electrical burns. The results in temperature rise at least, can be duplicated and improved on by the conditioned air cabinet (hypertherm of Kettering) and range downward through the use of cabinets and cradles with luminous bulbs to electrically heated blankets and finally to blankets heated by hot water bags and to the ultimate simplification of blankets alone with or without hot drinks. The bath technic of inducing fever has undergone particularly interesting and perhaps significant simplification by its application to the treatment of gonorrhea (Warren) in which

the patient is laid in an empty bathtub into which water is allowed to flow at a temperature ranging between 105 and 111 F When the water reaches the outlet level and the patient begins to feel the exhaustive and giddy symptoms which come on from dehydration and loss of chloride, he opens the outlet device, lets the water out, is dried retires to his bed on the ward and when his temperature under light covering is down to normal again he is ready to go about his ordinary business Apparently this type of fever jolt is capable of greatly increasing the effectiveness of the sulfonamides and its application to the treatment of syphilis may prove of much importance Dennie, Polsky and Lemoine (1930) reported good responses in late resistant and congenital syphilis by a similar technic. The more elaborate types of equipment, including the conditioned air cabinet, make perhaps, more provision for the comfort of the patient, but they require a highly specialized set-up and attendants whose skill must be proportional to the length of time that the patient's temperature is to be elevated. The self-recording rectal thermometer is probably as important as the body heating device itself since it makes possible accurate control of the temperature throughout the fever siege The patient escapes the discomfort and sense of prostration associated with foreign protein therapy It is important to maintain fluid and chloride levels and to watch for and avoid heat shock and prostration In the wider application of fever to the control of a disease like syphilis, simplification and elimination of complicated methods requiring treatment centers and special technical experience is the direction of progress.

Comparative Efficacy of Various Methods.—It is evident that too little is as yet known of the modus operandi of fever therapy to permit adequate comparison of the effectiveness of the various types of procedure. Much animal experimental work remains to be done and many years of evaluation of the long range effect of treatment for syphilis of which fever has formed a part. The impression is strong, with the authors at least, that malaria in late neurosyphilis and perhaps in congenital syphilis, and the physical methods in early and latent syphilis are, for a variety of reasons the preferred types of treatment today That such a statement today will necessarily hold tomorrow is too much to expect. The specific contributions of the Cooperative Clinical Group to the evaluation of this question in the treatment of neurosyphilis are summarized in Chapter XX

DOSAGE THEORY AND PRACTICE

The tendency to fall back on rules of thumb and a dosage scale in the treatment of syphilis is, of course inescapable and not to be too severely condemned. It is however necessary for one who would treat all aspects of the disease with discrimination to keep in mind a series of quasi-empirical maxims summarized briefly in Fig 65 which serve as a guide to the appropriate dosage for a given situation As regards the spirillicidal drugs especially one would imagine that the larger the dose and the higher the concentration of the medicaments brought into contact with the organism, the better the effect. Early studies of neoarsphenamine (Katz) suggested that this was not necessarily true, for half the full dose seemed to act as rapidly as the full dose In the production of non-specific effect whose importance in treatment as has been already stated seems to be on the increase rather than the reverse Toyama and Kolmer have shown that large doses of either arsphenamine r

mercury directly interfere with the nonspecific defence and diminish the production of agglutinins and lysins with which among other devices the body carries on its own fight against the invader Any considerable experience with the treatment by arsphenamine and mercury of other diseases besides syphilis confirms this experimental study by many clinical impressions. Large doses of arsphenamine have perhaps more prolonged spirillicidal effect, but the stimulation of general resistance seems to be lost when more than moderate dosage is employed The abuse of mercury by heroic dosage may also undermine the patient so rapidly that its good effects on the disease are lost in a general breakdown of resistance Thus far the tolerance to bismuth and the ability to stand large doses of it over long periods of time seem to surpass those of other antisyphilitic drugs.

Time-Dosage Relationships.—Experience with intensive methods for the treatment of early syphilis in animals, awaiting confirmation in man, has convinced Eagle and Hogan (1942) that within broad limits the curative dose of mapharsen with any one type of treatment is largely independent of the time period over which the treatment is given Their data suggest that repeated doses at short intervals are more effective than either one large dose or repeated doses at weekly intervals The total curative dose of mapharsen in rabbits was found within broad limits to be approximately constant, and since the total tolerated dose on any schedule of injections increases directly with the duration of treatment, they concluded that the margin of safety between the toxic and the therapeutic dose "chemotherapeutic index," may be increased continuously by prolonging the duration of treatment. An intensive treatment schedule as effective as twenty to thirty weekly injections of 60 mg (1 mg per kg) mapharsen and providing a comparable margin of safety would be at least approximated by (*a*) injections of 20 mg. mapharsen (0.3 mg. per kg) repeated twice daily for four to eight weeks (*b*) daily injections of 30 mg mapharsen (0 5 mg per kg.) continued for five to ten weeks or (*c*) injections of 60 mg mapharsen (1 mg per kg) repeated three times weekly for five to ten weeks The application of this theory to treatment for early syphilis is discussed in Chapter XIV

Prolongation vs Mass.—The Cooperative Clinical Group studies of the treatment of early syphilis apparently demonstrated a principle which it is important to bear in mind at a time when pressure is strong for the shortening and so-called intensification of treatment systems for early syphilis. From the CCG material (1932) it appears that the good results obtained by prolonging continuous treatment, for example for more than a year are more than double those obtained by continuous treatment for one year or less. Even irregular treatment gives three times as good results when applied for more than a year as it does when applied for less than a year Other criteria of favorable treatment effects bear out this relationship which may of course be due to the fact that prolongation of treatment is simultaneously an increase in mass, and brings about a closer and closer approximation to Eagle and Hogan's conception of the total curative dose at least of the arsenical. This has been estimated by Eagle and Hogan on the basis of their experimental work with rabbits as 1200 to 1800 mg of Mapharsen dosage determined by weight on the basis of 20 to 30 mg per kilo

Relative Effectiveness of Low vs High Dosage—While the question is complicated by differences in the therapeutic activity of various arsenicals and heavy metals and of individual lots of the same drug, it appeared from

the work of the Cooperative Clinical Group (Stokes, Usilton and coworkers, 1934) that there is definite evidence of the greater effectiveness of larger over smaller dosage scales In this study small dosage is rated as 0 2 to 0 45 Gm arsphenamine (606) and large dosage as 0 45 and over for men (0.3 Gm or over for women) The study indicated that large dosage does not cause any type of unfavorable outcome and that the smaller scale of dosage has definite shortcomings 7 6 per cent relapse or serologic fastness on the lower scale vs. none on the larger scale Nearly three times as much neurosyphilis develops on the lower dosage scale as on the higher dosage scale. Accordingly one of the genuine advantages of the intensified treatment systems will be their

Fig 65

SOME DOSAGE MAXIMS IN SYPHILOTHERAPY

1 Mak th first dose half or less than the prescribed maximum.
2. Follow this rule to avoid Herxheimer effect in ordinary cases when using shock-inducing drugs be doubl cautious if heart, nervous system, or special sense mechanism i involved.
3. Be even more conserv tiv if therapeutic paradox may develop.
4 Tak age, and weight into account. Sex as such is being increasingly disregarded
5. Learn schedule for children (see p. 275)
6. Persistence in underdosag (subtherapeutic doses) after the first treatment may activate and stir up or render refractory the early or latent case
7 Abrupt overdosag may sensitize or destroy tolerance (render patient reactive)
8 Long-continued overdosage produces accumulation, chronic intoxication, and injury t the eliminative mechanism
I drugs ith cumulative action, the larger doses and shorter intervals if used should be near the beginning (after the first) rather than toward the end of treatment season.
9 Use smaller dose when ( ) using short intervals; (b) seeking nonspecific effect ( ) treating the cachectic and the aged (d) in febrile states and intercurrent infections ( ) pregnancy (f) in organic disease (g) for tonic ction in lat infections (h) in serious visceral nd vascular impairment from syphilis ( ) when combining t o or more toxic drugs (including so-called combined treatment") in treatment (j) in the know hypersensitive or idiosyncratic patient.
10 Small dose courses should be long and repeated, and in the case of arsphenamines particularly demand heavy metal reinforcement t prevent activation nd relapse
11 Use larger doses when (a) using longer intervals, (b) seeking curative effects i early syphilis ( ) using the drug alone (d) treating the robust and fully developed individual.
12 In purely nonspecific therapy se moderat doses and longer intervals. Never base tolerance.
13 Th rate of accumulation and elimination and the routes for each drug used should be understood factors in determining dosage technic

a urance that the patient receives once and for all and early in the course of his disease the maximum dose that his weight will tolerate, and not any compromise with it dictated by a l w dosage scale or a lack of persistence in treatment.

Subtherapeutic Activation.—The risk of induction of arsenic-fastness and of therapeutic activation of the disease have been discussed by Beerman (1930) and by Milian. These observations are based on clinical experience nd on the laboratory ork of Bronfenbrenner and Schlesinger Klauder Brown nd Pearce and the clinical observations of Hoffmann and Milian. While such activation and resistance-inducing effects re comparat vely rare they are sharp w rning t the clinician t adhere t an adequate and if anything larger dosage scale scrupulously adjusted t eight and not t merely empirical standards, in the use of arsenical medication for the treatment of syphilis

THEORY OF THE REST INTERVAL

Intermittent *versus* Continuous Treatment.—The age-long battle between intermittence and continuity (no rest interval) treatment for syphilis is now approaching—if it has not actually reached—a decision in favor of the continuous side. Certainly in early syphilis the successful administration of total curative doses of neoarsphenamine and mapharsen in a single continuous procedure reduced to as little as five days without destruction of the patient has done away with many though not all of the toxicity objections to continuity in treatment. It is impossible any longer to sidestep the massive collection of statistical information represented by the studies of Moore and Kemp and the American Cooperative Clinical Group, as well as the League of Nations investigation in toto of the superiority of continuous over intermittent treatment in the early stages of syphilis. Granted that some form of therapeutic respite from the continuous administration of any one drug still has a tangible claim to consideration, ample provision for such respite can be made in the rotation or alternation of arsenical and heavy metal in all the current effective methods for the treatment of syphilis.

While such a statement is acceptable for early syphilis, late syphilis still remains a field in which impaired tolerance and constitutionally reduced resources may influence the choice between continuous and intermittent therapy. Here the rest interval may again come into its own. If nothing else the opportunity to recover from the toxic effects of treatment and to gain headway toward recovery from the disease by a succession of steps in which nonspecific processes probably play almost an equal part with the true specific or spirillicidal effects of treatment, can be observed at its best in the domain of late constitutional and particularly late neurosyphilis.

The so-called "intensive" (though comparatively speaking uniutensive or inadequate) systems of treatment such as those of Scholtz and Pollitzer, which have formed the basis of comparison with the Cooperative Clinical Group continuous material cannot be regarded as adequate examples of intensive treatment in the light of what is now becoming known about the massive dose or ultraintensified systems of intravenous drip and multiple injections given over five to ten-day periods. The older systems failed in that while they began intensively, they ended before the adequate total dose had been given, and interposed a rest interval for relapse before another fraction of the total dose was intensively administered. Apparently the eliminative mechanism for the drugs involved in the treatment of syphilis is adequate to practically any load placed upon it, even by the most intensive of present-day procedures, so that cumulative intoxication is rare, if it occurs at all, at least in the early phases of the disease.

COMBINED, SIMULTANEOUS, ALTERNATING AND OVERLAPPING TREATMENT

Combined Treatment.—Combined treatment is the term frequently used for a therapeutic regimen including two or more drugs or modes of attack in dealing with a syphilitic infection. Thus, the use of arsphenamine and mercury or arsphenamine and bismuth constitutes combined treatment. Such treatment, however, is not necessarily concurrent but may be alternate.

Alternate Treatment.—This is defined as combined treatment in which only one drug or method is used at any given time or in any given course, the next ensuing course employing another single drug or method of distinctly different qualities and potentialities. Thus, in combined arsphenamine and bismuth, the arsphenamine may be given alone in the first course, the bismuth alone in the second course, and on an alternating scheme arsphenamine alone

again in the third course and bismuth alone in the fourth course Simultaneous combined treatment would give arsphenamine and bismuth coincidentally as a single course and might then give one or the other drug alone in subsequent courses

Simultaneous *versus* Alternating Treatment.—Both continuous and intermittent treatment, since these two items concern the matter of rest intervals only may be given as combined simultaneous or combined alternating treatment.

Overlapping Treatment.—This is a compromise between concurrence and alternation. In an overlapping system a course may begin with an arsphenamine which is given alone for a variable number of injections and then given concurrently with several injections of a heavy metal The arsphenamine phase of the treatment then stops and the heavy metal is continued alone for a definite time to be again joined so to speak, by the arsphenamine before the end of the heavy metal course Thus the beginnings and endings of the arsphenamine and heavy metal courses overlap each other the treatment being both continuous, simultaneous and alternating in partial degree

The Combined Use of an Arsenical and a Heavy Metal.—The battle waged throughout the arsphenamine era between those who would depend exclusively on the arsenical (Leredde, arsphenamine 606) or exclusively on the heavy metal (Schwartz, bismuth) or in today's practice the proponents of the five-day drip and even the initial multiple injections systems (Hyman, Chargin, Leifer Eagle) is apparently in fair way to be won by those who support in one form or another the combined use of the two types of drug. Already students of hyperintensive treatment such as Shaffer are inserting bismuth into their multiple injection courses, and Moore Eagle and others, seeking to develop intensive systems in the interest of time-saving for the armed forces, are harking back to bismuth as the shortcomings of reliance on a single drug become apparent. The problem is by no means simple and the question of true synergism versus merely additive effects requires much further study Nonetheless, safe practice is definitely holding to the double life-line of two drugs used simultaneously concurrently or alternately with or without overlap. Thus it may still be announced as sound principle that an arsenical and bismuth treatment is to be preferred to either drug alone French experience, and the observations of the Breslau clinic during a period when treatment was restricted to bismuth, indicated the necessity for the arsenical from the standpoint of infection control, if not the cure of the disease It seems reasonable to believe that the Cooperative Clinical Group demonstration of the ultimate equality of effectiveness of the therapeutically less effective neoarsphenamine as compared with arsphenamine 606 was largely due to the supportive amplifying effect of the use of bismuth. The question of simultaneity as compared with alternation of administration seems in process of decision at this writing, in favor of alternation.

Kolmer has been able to demonstrate the marked stepping-up effect produced by the synergistic use in trypanosomiasis in rats of an arsphenamine with a comparatively ineffective mercurial. Both mercurophen and flumerin when administered with arsphenamine and neoarsphenamine markedly accentuated the trypanostatic effect, though both were used in lower doses than were required when the drugs were given alone Kolle obtained similar results in the use of neosilversalvarsan and novasurol in rabbits, and Voegtlin and Smith have observed the complementary action of arsenical and antimony compounds. Myers and Corbitt similarly reinforced the action of subeffective doses of neoarsphenamine with sodium and potassium tartro-bismuthate.

Schamberg (1929) and Harrison (1931) have for many years advised simultaneous arsenical and heavy metal therapy Bernard (1928) believed that concurrent treatment yielded less neuro recurrences and Lehnhoff Wyld (1924–1926) found the trypanocidal action of sulfarsenol was greater when any of a variety of other metals was in the circulation at the same time than when it was given alone Belding (1931) found that the serologic results were best when combined arsphenamine and mercury treatment was used in preference to either drug alone Belding's paper however, does not make it clear whether he used simultaneous combined or alternating combined treatment. In a careful experimental study on rabbit syphilis, Clausen, Longley and Tatum (1932) of the University of Wisconsin, using combinations, administered simultaneously of fractions of the minimum curative dose (M.C.D.) of an arsenical with fraction of the M.C.D. of bismuth

preparation, were ble to determine the quantitative nature of the combined therapeutic action of these two types of compounds. They found that it was one of simple addition rather than potentiation or inhibition. On the other hand, the cotoxicity of bismuth and arsenical compound was found t be less than additive nd that the cotoxicity of an arsenical with a more slowly beorbed bismuth compound is much less additive than with preparation more rapidly absorbed. These findings indicate t the Wisconsin group that there is greater margin of safety hen the drugs are used concurrently than when either is used alone in correspondingly effective doses.

On the other hand, there is much recent evidence t show the disadvantages of combined (simultaneous) treatment. In 1930 Beerman demonstrated what had been repeatedly emphasized before (Felke 1922 Schreus, 1923 Hoffmann and Schreus, 1923 Szecsi, 1923) that bismuth had some restraining effect on the serologic action of the arsenical. This was confirmed in more extended series by Beerman (1932). This effect, however may be due to reduced dosage or because of inferior drug. Beckh and Barnett (1930) made the more significa t observation that the incidence of relapse both clinical and serologic as greater among patients given concurrent treatment. Beckh and Kulchar (1939) from their experience with 18 patients resistant to three different arsenicals, including arsenoxide (mapharsen) found that more cases occurred after combined (simultaneous or concurrent) than after the alternating plan of treatment. Furthermore in spite of the definite theoretical adva tages of combined over alternating treatment, practical experience has forced us to abandon the former and accept, as standard American practice the alternating system of treatment (with overlap)

THE "ARSENICAL RULES

From the foregoing consideration it is now permissible in the light of the present-day knowledge of the mode of action of arsphenamines and heavy metals, to propose four great and practically inviolable rules governing the employment of the trivalent arsenical group of drugs in the treatment of syphilis.

Rule I.—Never use an arsphenamine exclusively or end a course of treat ment with it. Always use a heavy metal in conjunction or sequence.

Rule II.—Never use an arsphenamine insufficiently—that is, in a single short course Either give a long course of the drug or if short courses seem more advantageous, cover the possibilities of relapse thoroughly by the use of a heavy metal. The short, single course of arsenical early or late in the disease not properly combined with or followed by heavy metal, is too apt to give all the disadvantages and none of the advantages of this group of drugs.

Rule III.—Use an arsenical with utmost caution, and initial very low dosage and gradual increase when there is reason to fear either therapeutic shock or therapeutic paradox. Preferably prepare the way with a heavy metal (see p 220) always reduce the initial dose of arsphenamine to one half the full or adult dose or even less and do not use an arsphenamine at all in the late case until, if ever it is possible to envisage clearly a lasting beneficial effect.

There is an increasing tendency th the advent of mapharsen, t disregard, belie prematurely this rule

Rule IV —Never use an arsphenamine in a therapeutic test for diagnosis where its nonspecific effect, by producing improvement in other conditions may lead to confusion of diagnosis with respect to syphili

PRINCIPLES UNDERLYING THE THERAPEUTIC TEST FOR SYPHILIS

Rul IV Elaborated.—The therapeutic test is so closely related to the treatment of syphilis and to both its specific and nonspecific effects, that the following summary of its principles is given

again in the third course and bismuth alone in the fourth course Simultaneous combined treatment would give arsphenamine and bismuth coincidentally as a single course and might then give one or the other drug alone in subsequent courses

Simultaneous *versus* Alternating Treatment.—Both continuous and intermittent treatment, since these two items concern the matter of rest intervals only may be given as combined simultaneous or combined alternating treatment.

Overlapping Treatment.—This is a compromise between concurrence and alternation In an overlapping system a course may begin with an arsphenamine which is given alone for a variable number of injections and then given concurrently with several injections of a heavy metal The arsphenamine phase of the treatment then stops and the heavy metal is continued alone for a definite time to be again joined so to speak, by the arsphenamine before the end of the heavy metal course Thus the beginnings and endings of the arsphenamine and heavy metal courses overlap each other the treatment being both continuous, simultaneous and alternating in partial degree

The Combined Use of an Arsenical and a Heavy Metal.—The battle waged throughout the arsphenamine era between those who would depend exclusively on the arsenical (Leredde, arsphenamine 606) or exclusively on the heavy metal (Schwartz, bismuth) or in today's practice the proponents of the five-day drip and even the initial multiple injections systems (Hyman, Chargin, Leifer Eagle) is apparently in fair way to be won by those who support in one form or another the combined use of the two types of drug Already students of hyperintensive treatment such as Shaffer are inserting bismuth into their multiple injection courses, and Moore Eagle, and others, seeking to develop intensive systems in the interest of time-saving for the armed forces, are harking back to bismuth as the shortcomings of reliance on a single drug become apparent. The problem is by no means simple and the question of true synergism versus merely additive effects requires much further study Nonetheless, *safe practice is definitely holding to* the double life-line of two drugs used simultaneously concurrently or alternately with or without overlap. Thus it may still be announced as sound principle that an arsenical and bismuth treatment is to be preferred to either drug alone French experience and the observations of the Breslau clinic during a period when treatment was restricted to bismuth, indicated the necessity for the arsenical from the standpoint of infection control, if not the cure of the disease It seems reasonable to believe that the Cooperative Clinical Group demonstration of the ultimate equality of effectiveness of the therapeutically less effective neoarsphenamine as compared with arsphenamine 606 was largely due to the supportive amplifying effect of the use of bismuth. The question of simultaneity as compared with alternation of administration seems in process of decision at this writing in favor of alternation.

Kolmer has been able to demonstrate the marked stepping-up effect produced by the synergistic use in trypanosomiasis in rats of an arsphenamine with a comparatively ineffective mercurial. Both mercurophen and flumerin when administered with arsphenamine and neoarsphenamine markedly accentuated the trypanostatic effect, though both were used in lower doses than were required when the drugs were given alone Kolle obtained similar results in the use of neosilversalvarsan and novasurol in rabbits, and Voegtlin and Smith have observed the complementary action of arsenical and antimony compounds Myers and Corbitt similarly reinforced the action of subeffective doses of neoarsphenamine with sodium and potassium *tartro-bismuthate*.

Schamberg (1929) and Harrison (1931) have for many years advised simultaneous arsenical and heavy metal therapy Bernard (1928) believed that concurrent treatment yielded less neurorecurrences and Lehnhoff Wyld (1924–1926) found the trypanocidal action of sulfarsenol was greater when any of a variety of other metals was in the circulation at the same time than when it was given alone. Belding (1941) found that the serologic results were best when combined arsphenamine and mercury treatment was used in preference to either drug alone Belding's paper however does not make it clear whether he used simultaneous combined or alternating combined treatment. In a careful experimental study on rabbit syphilis, Clausen, Longley and Tatum (1942) of the University of Wisconsin, using combinations, administered simultaneously of fractions of the minimum curative dose (M.C.D.) of an arsenical with fraction of the M C D of bismuth

not discharge it completely or sometimes even partially by the most detailed and painstaking instruction of the patient.

The facts involving the cooperation of the patient are included in Figure 212. Two studies of infectious relapse from the standpoint of physician-patient responsibility undertaken in our clinic have indicated that responsibility for lapse in treatment, which is the usual starting point of infectious recurrent lesions, is approximately equally divided between physician and patient.

Failure to inform the patient fully of the facts; unwarranted assurances based on the first or subsequent negative serologic tests; survivals of the conception of abortive cure leading to shortened treatment, and frank ignorance of the management of syphilis by modern methods were the items in the bill against the physician. In the analysis from the patient's standpoint by Pugh, Brown *et al.*, *failure to realize the seriousness of the disease* ranked with the discomforts of reaction to treatment as the *foremost* of the reasons *for failure to* carry treatment through to discharge. The worth of ethical pressure, while often overestimated, is by no means to be despised, and the wise and effective physician treating a patient to control infectiousness, spares (or extension of time between date of infection and the patient's resumption of sexual activity by every device known to the temple, the court, and the sawdust trail. When once, in his best judgment, the physician has authorized sexual activity, he should strive to keep check upon it, in the early years particularly, limiting it to the times when the patient is under arsenical control, if possible.

THE CONTROL OF INFECTIOUSNESS IN SYPHILIS

A Résumé of Known Principles

Because of its importance in the control of syphilis as a disease, and especially because of its significance in marriage and prenatal testing law decisions, the following summary of existing knowledge regarding the control of infectiousness in syphilis is prepared.

1. *The person with infectious syphilis has acquired the disease from another in the same condition, and will, in all probability, pass it on to an uninfected person.* This then, is the first principle of the epidemiology of syphilis, and the first principle of its control is that *contact should be traced both ways, to and from the infectious case.* The technic of contact-tracing, while to some extent a matter of individual interest and aptitude on the part of the physician who first sees the infectious patient, can also be turned over to trained public health nurses who will conduct the work in a manner that can give no offense to any reasonable physician or patient. *The State Division of Syphilis and Genito-infectious Diseases is prepared to provide contact-tracing and follow-up service on request, for any physician.*

2. It is critically important to remember that *blood tests for syphilis do not identify, define or have any necessary relation to the infectiousness of the disease.* In the chancre stage, and infectious relapses later in the course of the disease among certain patients, serologic tests may be occasionally, frequently or constantly negative, yet the disease be actively transmissible. The reverse statement is equally true that the serologic tests may be occasionally, frequently or constantly positive without any infectiousness whatever. This is especially true of late latency, late visceral, vascular and neurosyphilis, and congenital or prenatal syphilis.

3. *There are no absolute rules or statements with regard to infectiousness to which occasional exceptions may not be found.* It is necessary therefore, to be on guard constantly for the possibility of infectiousness, even where it seems unlikely, and absolute statements with regard to non-infectiousness should be made with caution and with due regard for their probable, rather than absolute, character.

4. *Time and treatment are the controlling elements in the infectiousness of the disease.* In terms of stages, the primary, secondary and early latent periods are those of maximum infectiveness. Considered in terms of time, current evidence tends to indicate that 84% to 97% of the infectious lesions of the disease occur within the first two years. On the other hand, closer observation and study of relapse and recurrence may necessitate some revision of this statement in terms of patients who remain infectious for from five years to a decade or more.

5. *Infectiousness in prenatal or congenital syphilis is confined* for practical purposes and so far as present knowledge goes, to the eruptive manifestations of the first year of life. The male

Reprinted from "Pennsylvania Health," Vol. 1, No. 2, April, 1940.

*

congenital syphilitic passes rapidly into the category of late syphilis, so far as transmission of the disease is concerned, and as a child, adolescent, and adult, does not so far as is known, transmit the infection. The female congenital syphilitic, even though untreated, transmits the infection to her partner only with the greatest rarity and practically never to her child. Third generation syphilis is among the reportable rarities of the disease. In any event, adequate treatment for prenatal syphilis should offer full protection.

6. *While infectiousness in late latent and late active syphilis is accepted as extremely rare*, infectious transmission has been recognized in a paretic as long as twenty-six years after infection. It must be apparent therefore that *the history of an individual patient with reference to relapse is an important consideration in deciding the probabilities in his case.*

7. *Infectiousness in women has some important special phases.* First, the onset of the disease, and even quite a proportion of the secondary manifestations occur in the genital tract where they are invisible to the patient, and not searched for by the physician. The Negro woman is particularly known for her predisposition to mucocutaneous infectiveness. It may be obvious therefore, that control of infectiousness as a public health problem in syphilis will have much smaller possibility of success through the attempt to recognize and control this status in women than it will in men. *Every effort should be concentrated therefore not only upon the adequate examination of the female patient for infectious lesions but upon the control of infectiousness in the male.*

Relatively little is known of the carrier stage of infectiousness in women (i. e. infectiousness during latency). The female genital tract may conceivably serve as a carrier of infective material even in a patient who is not outright infectious by virtue of her own disease.

8. *Infectiousness of the Pregnant Syphilitic Woman for her Child.* The intimacy of the inter changes between mother and fetus, notwithstanding the probable partial value of the placental barrier makes infectiousness in the woman from the standpoint of the child so unamenable to rules or categorical statements that *current practice accepts the necessity for anti-infectious treatment of the mother during pregnancy as routine for the protection of her unborn child.*

9. *The infectious lesions of syphilis are largely those of the mucocutaneous surfaces.* Lesions intrinsically non-infectious at the start may become so through erosion, even on the glabrous skin, and in the folds of the body. The mucous patch and the eroded or hypertrophic papule (the latter constituting the flat condyloma, so-called), all of these lesions characteristic of the secondary stage and the relapses of the early latent period, are particularly menacing because of their transient and symptomatic character, their easy confusion with other conditions, and the ease with which they are overlooked altogether in casual examination and in sexual contacts. The primary lesion of syphilis is infectious from the start and may even through erosion in coitus or otherwise after it has actually healed, again become a source of infection. It should be recalled that the primary lesion of syphilis may be inconspicuous and fail entirely to attract the attention of the patient, and even the physician. The primary lesion in the *female* has the reputation of being particularly evanescent and inconspicuous.

10. *The presence of the Spirochaeta pallida can be demonstrated in many lesions* in which it is hardly customary as yet to institute darkfield examinations. Papular lesions about the genitalia which are not actually eroded or condylomatous, can be scraped and examined by darkfield often with convincing demonstration of the organism. On the other hand, it is important to remember that saprophytic spirochetes are common in both the mouth and genitalia, and such examination as the darkfield should be expertly interpreted. *Kits for the collection of such material are supplied by the State Public Health Laboratory on request, and examination of material collected in accordance with directions will be promptly reported.*

11. *The infectiousness of blood, secretions and exudates* is probably not as great as is often believed. On the other hand, any secretion, excretion or discharge which passes over an infectious lesion may contain *Spirochaeta pallida*, and such fluids as blood, breast milk and the like may contain the organism so erratically and unpredictably that their infectiousness during the infectious period of the disease should be more or less taken for granted. This is particularly true in operative and transfusion work and in injuries to physicians or other personnel involving needle-pricks with infectious blood contamination, droplet or contact contamination and so forth. *The State Division of Syphilis and Genitoinfectious Diseases will advise by wire, collect, on request, as to the course to be pursued in an individual case in which it is feared that the disease has been transmitted by infective material of this kind.* The necessary information to be supplied with the inquiry is as follows.

1. Description of the accident, including handling of the infective agent before, and after.
2. Description of the source of infected material, including evidence of the disease, and stage or duration of the infection, if a patient.
3. Any previous treatment of the infective source or patient with dates.
4. Treatment given the victim of the accident.

12. *The infectiousness of semen* has not thus far been finally evaluated, and it is certainly much less than has been believed. It is not believed at the present time that syphilis can be transmitted to the ovum by semen of an infected male. This disposes for the time being of the conception of paternal transmission to the child via an uninfected mother.

13. *Physical conditions for infection transmission in syphilis* are difficult to define and contain many elements of the unexpected. Where it is feared the disease has been transmitted it may not be, and conviction of absolute safety or unawareness in a given situation is often at the bottom of an infection. No absolutely dry material can transmit the disease. Moisture and relative anaerobiosis appear to be necessary conditions. Refrigeration does not destroy the organism for a considerable period, so that autopsy material may be dangerous. A fluid containing organisms deposited upon a moist surface offers the maximum risk of infection. For that reason, in practice, kissing and sexual intercourse are the primary modes of transference. Glasses, pipes, silverware, razors, may function in this way. Bizarre intermediate transmission is not excessively rare, and the picking up and inflation of a condom on the street has been known to lead to primary infection in a child. Dishes, glasses, and similar intermediary materials, if thoroughly washed in hot water and soap do not transmit the disease.

14. *General Precautions against Infectiousness.* The infectious lesions of syphilis can be made less dangerous, first, by reducing their frequency; second, by instructing the patient regarding their whereabouts and appearance, and third, by impressing upon him from the start, the importance of his cooperation in treatment regularity. Infectious lesions are relatively common in some patients; relatively rare in others, but unfortunately, except for the racial difference previously mentioned, no means of predicting with accuracy the tendency to infectious lesions in an individual case exists. *Observation of the patient, however, over a period of months,* offers the following guides:

1. *Very early reversal of the serologic test* for syphilis under treatment (negative blood before the eighth week) is indicative *of a relapsing tendency,* possibly infectious.
2. *Slowness in resolution of infectious lesions,* particularly the chancre, is a warning of infectivity due to treatment resistance. Every patient under treatment for early syphilis should be closely observed for the rate at which lesions heal. The physician will occasionally be surprised by the failure of an active arsenical to cause involution of obviously infectious lesions, not only after one or two, but after many injections.
3. *Dirt and irritation locally,* whether in the mouth or about the *genitalia,* favors the production of infectious lesions.
4. There is reason to believe that *the free use of alcohol* has some tendency to predispose towards relapse.
5. *The seropositive primary stage of syphilis,* before the development of secondaries, which is the stage of the disease in which most infection tends to be discovered at the present time, is the most prone to relapse under treatment of any aspect of the disease. Accordingly *patients who begin treatment with a seropositive chancre before the appearance of secondaries, must be especially warned,* especially supervised, and receive especially prolonged treatment with special regularity if their infectiousness is to be adequately controlled.
6. *The smoking and chewing of tobacco has been known* for many years to predispose to the development of infectious lesions in the mouth.
7. Since the infectiousness of semen and of vaginal discharges is not clearly understood, the use of a condom in coitus should be uniformly advised for all persons within the average infectious period *of* the disease, and for all persons exposing themselves sexually to risk of infection.

TREATMENT CONTROL OF INFECTIOUSNESS

1. It should be emphasized that no amount of instruction to the patient and no amount of pains and particularly in examination on the part of the physician can take the place of effective modern treatment in the control of infectiousness in syphilis. In fact, *through contact-tracing of the infectious person and treatment control of infectiousness itself lies the only existing avenue to the control of the disease.*

The following briefly summarizes the principles involved: ( ) infectiousness in syphilis is controlled by the arsphenamines and arsenoxide, *and by no other drug or treatment with even approximate effectiveness.* These drugs should therefore form an integral part and in general, the initial part of the treatment of all infectious or potentially infectious persons. The dosage of these drugs must equal or exceed a minimum of 0.3 gram neoarsphenamine or arsphenamine and 0.05 gram of arsenoxide (mapharsen) if infectiousness is to be controlled in the average adult, and the dose

should be rapidly increased to the therapeutic maximum. Do not begin treatment with minute doses, for treatment-fastness may result. (b) *The heavy metal element in treatment*, including bismuth and mercury (preferably bismuth) *is useful in combination with the arsenical, but ineffective alone in controlling infectiousness* If an arsenical cannot be used (and this is exceedingly rare) water soluble heavy metal salt such as sodium bismuth tartrate or mercury dichloride or succinimide given frequently intramuscularly is the best heavy metal choice for the control of infectiousness. All other heavy metal preparations are to be regarded merely as adjuncts in infection-control and not as mainstays. ( ) *T factors are of vital importance in the arsenical control of infectiousness: first, regularity and continuity of treatment, and second amount and duration of treatment.* An enormous decrease in the percentage of infectious relapse follows as little as five to nine weeks of arsenical treatment in effective dosage. On the other hand, to obtain anything even approximating reasonable public health standard of infection-control, not less than 20 intravenous arsenical injections are necessary accompanied by corresponding number of heavy metal injections, preferably bismuth. This estimate of "20-40, originally measure of statistical convenience has had considerable publicity as minimal standard in treatment for non-infectiousness. N conclusive evidence exists that this minimum amount of treatment is adequate. (d) *Treatment to non-infectiousness, while recognized public health desideratum*, has no *absolute standards of time, dosage or number of treatments*. In fact, it is impossible to define form or amount of treatment which absolutely insures non-infectiousness. For that reason it is advised that the physician treating patient for the control of infectiousness, *aim at the standard for cure rather than at anything short of it*.

2. *Both in treatment for the control of infectiousness, and in treatment for cure, absolute continuity without lapse or rest interval has* been proved both by international and American investigations *to be the optimum procedure*. The introduction of lapses, for which the patient is responsible or rest periods, permitted by the physician, enormously increases the risk of relapses, of treatment fastness, and ultimately uncontrollable infectivity

3 *The amount of treatment now recognized as reasonable standard* is defined as thirty intravenous injections of an effective arsenical in effective dosage; sixty intramuscular injections of an effective bismuth salt (for example, bismuth subsalicylate) distributed in alternating courses over period of not less than one year followed by two years of treatment observation. This statement is subject to modification dependent on the development of the still experimental systems of intensive treatment (see Chapter XIV) This constitutes treatment aimed at cure, and is recommended the ideal for the control of infectiousness. Where this ideal cannot be attained, the largest number of arsenical and heavy metal injections in effective dosage and continuously given, over the longest period of time should be the practical goal

4 *The control of infectiousness in early latency* (first four years of the disease) requires treatment approximating that for primary and secondary syphilis. In the later years of latency the public health standard calls for approximately 24 injections of the arsenical and much more prolonged use of heavy metals (approximating 80 to 100 injections) for best results.

5 *A recommended standard of treatment for patients seen in the seropositive primary stage* (more resistant and prone to relapse than other early stages) is 40 intravenous injections of the arsenical, with 60 injections of the heavy metal. Especially close observation during the post treatment period of probation in such cases is desirable.

6. *Control of infectiousness pregnancy* cannot be made matter of rule but continuous treatment throughout the pregnancy approximating ten intravenous injections of the arsenical and ten intramuscular injections of oil-suspended bismuth salt (preferably the subsalicylate) is satisfactory average requirement. Its applicability is of course conditioned by the circumstances of the individual case but continuity without lapse or rest intervals, and the termination of treatment just before term with an arsenical rather than heavy metal are essential.

7 *Serologic Relapse and Infectiousness* While early reversal of positive blood test to negative may arm of relapsing or treatment resistant tendency and while fluctuating serologic tests during intensive treatment also indicate resistant infection, both physician and patient should be cautioned not to accept one or many negative tests as evidence of non-infectiousness, or at the other extreme to interpret fixed or treatment-resistant positive as necessarily evidence of infectiousness Time and the character amount and regularity or continuity of treatment, together with the recognized course of the individual patient case under repeated observation, are far more important guides.

8. *The foreshortened intensive (1–5 day and 12–26 week) systems* of treatment for syphilis ordinarily render the patient noninfectious in the same time as that required by the longer standard systems. There exists, however because of the early discharge of the patient while he is still within the theoretical period of greatest probability of infectious relapse very serious problem calling for the closest follow up of the once completely treated and asymptomatic patient.

Observational Control and Infectious Relapse *vs* Reinfection under Intensive Systems.—Proponents of intensive systems are apt to lose sight of the obligation to maintain two years minimum check on the recurrence of infectious lesions in their patients and in any event the observation to which such patients are subjected will not be as intensive as the week-to-week check that can be maintained on those who follow strictly the requirements of the longer standard systems. The observed great increase in frequency of so-called "reinfection" in patients who have been treated by the foreshortened intensive technics arouses the suspicion that these patients are in reality the victims of infectious relapse rather than reinfection and emphasizes the redoubled necessity for observation and caution in interpretation. For statistical purposes in evaluating these methods with reference to the control of infectiousness, reinfection which is notoriously difficult to prove, should be set aside in favor of the interpretation of infectious lesions observed after intensive treatment, as *relapse*. The disposition to relax the existing criteria of reinfection in order to put a better face on possible relapse following intensive systems, is to be regretted.

The transmission of syphilis in industrial relations as such is probably of small moment. Where the sexes work in contact, it is more important to attack the social hygiene problem than the epidemiological one through the instrumentality of matrons, effective shop discipline education. Even in food handlers and cosmetic workers (see Chapter XXIII on Public Health) the risk of transmission in syphilis may be exaggerated though it is true that one sometimes shivers when he watches the technic of barbers dining-room, kitchen and soda-fountain help from behind some scenes. Periodic serological testing of such persons is probably desirable for detection purposes. The most tragic aspect of the matter is the least known—the children infected by irresponsible and immoral servants in the home. We have seen everything from tabes in the house-mother of a great girls school dormitory to a chancre on the penis of a two-year old-baby traced to the activities of the crooked and infected nurse. Here at least is a field that merits genuine effort at study and control and one to which the physician alone in contact with the family life has real access.

ROLE OF TECHNIC AND CHOICE OF METHOD

"Smoother Treatment."—Hurting the patient in any therapeutic procedure is, in cumulative effect, a serious matter. The things that the dull needle, the mishandled spinal puncture and the lumpy painful butt do daily to the effective treatment and the hope for extermination of syphilis, have never yet been successfully estimated. Side by side with technical adequacy must go the thorough familiarity of the physician with his drugs. Grave injury and death lurk along the border of a modern course of treatment, waiting to take advantage of seemingly the most trifling oversight. No apology therefore need be made for commending technical perfection as described later to the physician who expects to treat syphilis effectively.

Systematized Treatment. Some Principles Governing Choice.—In connection with an attempt at evaluation of foreshortened intensive systems of treatment for early syphilis, a statement of principles was drawn up (Stokes 1942) which has more or less general application to the choice of treatment methods in their relation to morbidity mortality control of infectiousness and cure.

1 Syphilis cures itself or at least comes to seronegative arrest with little damage, in an unknown percentage of cases, probably ranging around 40 to 50 per cent.

2 A relatively small amount of treatment, if it does not of itself bring on relapse in one form or another through disturbance of the defense and immunity reactions is capable of raising the expectancy of cure to an unknown but considerable degree. *In seronegative primary syphilis this may well be guessed* to be as high as 70 per cent, to judge by the good results so widely reported for the now out of date "abortive cure systems.

3 Any system no system and even no treatment at all in syphilis has a running start toward cure, then The intensification and the prolongation of treatment that expresses itself in 1200 milligrams in five days or thirty arsenical and sixty bismuth injections in eighteen months is directed at a relatively small segment of unpredictably resistant infections These resistant infections will either (*a*) maintain the reservoir of infective disease by relapse, (*b*) be responsible for infected children or (*c*) lead to serious consequences especially in the cardiovascular and nervous systems of adults

4 Any new systems proposed should be judged basically by their ability (*a*) to equal or surpass the curative" expectancy of the old ones, (*b*) to lead to less infectious relapse (*c*) to cure more mothers and protect more children, (*d*) to reduce the incidence of cardiovascular and neurosyphilis and (*e*) by their relative risks to the patient.

5 For the evaluation of a system, time and observation are necessary to establish reduction of or absence of relapse and progression. For the former two to four years, for the latter up to ten years is a reasonable observational requirement. For decision on relapse the patient must be repeatedly and frequently observed, for it is a come and go affair For the evaluation of "cure" from a decade to a lifetime the longer the better is required

6 A system which under such scrutiny has shown itself at least equal to its predecessors may then proceed to claim additional advantage and support for a variety of reasons including cheapness rapidity controllability of the lapse factor because the whole job is finished in a short time and in the widening of availability of treatment by making possible the treatment of more persons per unit of time, personnel and equipment. Such considerations are in the main secondary to those of control of infectiousness and real curative power

7 If the new system equals the old or surpasses it in all these particulars it has but one more hurdle to make before achieving priority While *primum non nocere* is losing some of its meaning in a war torn world there are still arch conservatives who are inclined to examine critically the bad effects, the complications of a system. Of real importance to the victim are the risks involved the chances of damage or of death from treatment in the case of a disease which with none or very little treatment gives the victim at the outset a 40 to 70 per cent chance of escape from serious consequences. If an equal chance of escape with an older method offering less risk exists, only the most cogent reasons and a free choice by the patient justify the selection of the more dangerous method

What is an experimental method? A method remains in the experimental zone syphilotherapeutically speaking (*a*) until everything that can be found out on animals has been found out, including the direct effects on both the disease and its carrier of the method itself actually applied While the results

of trial on animals may prove disappointing equivocal and for various reasons inapplicable to man methods must be tried on animals to see whether the results are interpretable or not. (b) The method must next be applied to man using the lessons learned from animals. (c) When thus applied the method must now show its morbidity and mortality for man clearly and unmistakably and (d) its efficiency in man must be judged by the criteria enumerated

SEROLOGICAL CONTROL OF TREATMENT

In order to provide at this point, among the principles of treatment, a résumé of the many considerations bearing upon serological control, Fig 66 has been prepared as a semischematic and to some extent unavoidably dogmatic itemized statement of current conceptions. The detail of the response of serological tests to treatment was discussed at considerable length in the preceding chapter (IV) and the reader is urged at this point to combine the foregoing summary with the material just mentioned in a thoroughgoing review of the principles involved inasmuch as they are essential to all discussion of treatment in subsequent special chapters.

THE GENERAL RESPONSE AND PROGNOSIS OF SYPHILIS UNDER TREATMENT

Symptomatic Results of Modern Treatment.—The treatment of syphilis, to one at all initiated is one of the truly consoling and gratifying phases of the medical art. It is seldom indeed that the physician discovering syphilis in a symptomatic complex, does not draw a breath of relief and congratulate the patient on what might seem to the victim to be a subject for condolence instead The conditions that make no response to treatment in syphilis are almost nonexistent. Primary optic atrophy and the advanced well-established cases of tabes dorsalis, together with the effects of old chorioiditis, eighth nerve deafness and the irreparably damaged heart and vascular system, are almost the only phases of the disease in which the skilled therapist is as yet unable to justify himself Skill unquestionably plays a part in the consummation of this optimistic prognosis and an inappropriate selection of methods is sometimes all that is required to bring on disaster instead of relief A temporary good effect, as in the therapeutic paradox, may be replaced by ultimate catastrophe under injudicious management.

At the risk of drawing the fire of ridicule from our syphilological colleagues who appreciate the speculative intuitive intangible and uncontrollable factors in such a tabulation and the inner meaning of the ranges of variation involved, we present a summary of average expectancy in therapeutic results as we have seen them obtained by the standard methods dealt with in this book (Fig 67) The tabulation should be read as follows

"Acute interstitial keratitis 25 to 50 per cent improvement is expected in four to six weeks therapeutic effect ranging from 20 per cent impairment (−20) to 80 per cent improvement is to be expected in average cases within from four months to two years 60 per cent of cases achieve good results."

The occasional brilliant result or exceptional failure is not included in the estimates.

A percentage of −100 means an absolutely bad result, or death when the lesion can be a cause of death. The immediately fatal result may of course be averted in most cases by careful management, but the late deaths express the therapeutic paradox discussed in subsequent chapters The "minus 20

Fig 60.

THE SEROLOGIC CONTROLS OF TREATMENT—A SUMMARY OF PRINCIPLES

1 Never deify th serologic record of case ("paper syphilis) in treatment or mistak the test for the disease
2. Never use a serological test alon treatment guide in early syphilis or the only deciding point t y time
3. Use every effort t make diagnos and begin treatment i earl syphilis before the patient becomes seropositive This is the "Golden Opportunity
4. Treat early syphilis to an empirical maximum by system regardless of serological response treat late by the stat of the patient as whole
5 In all pparently seronegative primary syphilis, repeat the blood serologic test on the first or second day following the first arsenical injection. If positive regard the case seropositive primary instead of seronegative.
6 Place no reliance whatever on serological results grades t infectiousness (except warning of impending or actual relapse) i known syphilitic persons.
7 Avoid taking test before the 15th to 20th arsphenamine injection in early syphilis unless certain that the patient will continue if negative ("fiscal landmark")
8. In foreshortened intensive (five-day to ten-week) systems for early syphilis, quantitative serologic tests should if possible be employed t follow the titer of reagin during the period of observation after the completion of the treatment course
9 A too easily reversed serological test especially in early syphilis may indicat relapsing tendency and a poor defence.
10. Weak positive tests are important in early syphilis.
11. Irreversible positives require ( ) spinal fluid examination (b) lifelong observation with ( ) yearly complete syphilological ppraisal.
12. Asymptomatic fixed positives must be judged by their time factors and given treatment in general for protection against possibilities. Avoid activating quiescent infection by inadequat or unsupported treatment.
13 A fixed positive need not mean danger or death.
14. False positives, strong or weak, may occur in treatment as in diagnostic work.
15. Watch th heart and liver in an early case marked by occasional slight positive recurrences in series of negatives.
16. When treatment is suspended take tests as often in early cases patient will permit (at least quarterl) in lat cases indicated.
17 A provocative procedure if negative is no proof of cure, cannot detect an uncured case
18 It may be necessary to treat a persistently seronegative case because symptoms progress under cover of negative serology
19 In the presence of signs or suspicion of serious lat syphilis, even though seronegative begin treatment th heavy metal.
20. Place no early case on rest period or lat case on observation ithout spinal fluid examination if obtainable
21. Try to secure spinal fluid examination at least bet een the sixth t t elfth month of an early infection, and repeat in one year if negative
22. In asymptomatic latency where the positive blood test has made the diagnosis, never if voidable begin treatment without trying t obtain spinal fluid examination. If unobtainable begin treatment ith heavy metal, not arsphenamine
23. Remember th slight rise in cell count, and the red flag (preparetic) picture in the spinal fluid (pp 118, 119)
24. Sensitive test procedures are allowable treatment control
25 Both complement fixation and precipitation types of test should be sed The Kolmer W ssermann modification and flocculation procedures re ommended covering each other d screpancies.
26. Discrepancies (serological discord) are to be expected in lat and treated cases.
27 N series of negatives can exclude the need for spinal fluid control in treated cases.

NO SERIES OF NEGATIVE TESTS ALONE CAN EVER MEAN "CURE.

Fig. 67

ESTIMATED AVERAGE RATES AND DEGREES OF COMBINED SUBJECTIVE AND OBJECTIVE RESPONSE IN VARIOUS TYPES OF SYPHILIS UNDER MODERN METHODS OF ARSPHENAMIN AND HEAVY METAL TREATMENT

Lesion.	Improvement Expected. Per cent.	Improvement Expected. Time in which this improvement may be expected.	Ultimate Therapeutic Result Expected. Per cent.	Ultimate Therapeutic Result Expected. Time for maximum result.	Ultimate Therapeutic Result Expected. Per cent. of cases yielding good results.
Lues I, chancre	20 to +10	Spirochaeta pallida destroyed 21 hrs.	[illegible]	[illegible] days	100
Lues I, induration	[illegible]–60	11 days	100	3–6 wks.	100
Lues I, adenitis	50	3–4 wks.	80 to 100	6 wks.–4 mos.	90
Lues II, macular	70	48 hrs.	100	3–4 days	100
Lues II, papular	50	10–20 days	100	4–8 wks.	100
Lues II, pustular	50	10–30 days	100*	4–8 wks.	100*
Lues II, rupial	70	10–20 days	100*	3–8 wks.	100*
Lues II, mucous patches	70	24–48 hrs.	100	3–6 days	100
Lues II, condylomata	0–10	Spirochaeta pallida destroyed 21 hrs.	100	10 days–4 wks.	100
Lues II, periostitis	20	Pain relieved 24–72 hrs.	100	2–3 weeks	100
Lues II, adenopathy	20	2–3 weeks	50–100	6–12 mos.	90
Lues III, nodular	20	2 weeks	100	4–6 weeks	100
Lues III, ulcerative	20	3–4 weeks	100*	3–6 weeks	100*
Late bone lesions	40	3–4 weeks	100*	3 wks.–4 mos.	100* (non-[illegible])
Osteitis of skull	70	4–6 weeks	90 to 100	2 mos.–1 yr.	90* (surgical)
Palate and septum	25 to 40	2–6 weeks	60 to 90	3 mos.–2 yrs.	60–80
Throat and tongue (late)	70	8–15 days	60 to 100*	3 wks.–3 mos.	80–90
Acute interstitial keratitis	25 to 50	4–6 weeks	−20 to +80	4 mos. to 2 yrs.	50–75
Early optic nerve disease	[illegible] to 25	4–6 weeks	0 to 75	4 mos.–2 yrs.	25
[illegible] neurosyphilis	25 to 50	2–6 weeks	60 to 80	3 mos.–1 yr.	70
[illegible] (active)	70	24 hrs.–1 [illegible]	50 to 100	[illegible] wks.–6 mos.	
Liver and spleen early and latent	50	6–12 wks.	90 to 100	3–12 mos.	95
Hepatitis, late	20 to 50	6 mos.–1 yr.	50 to 100	2–3 yrs.	
[illegible], late	20	4 mos.	50 to 75	1–3 yrs.	
Aortitis, early	25 to 50	3–6 mos.	20 to 50	1–3 yrs.	70–80
Aortitis, late	0 to 25	6 wks.–6 mos.	0 to 75	1–3 yrs.	20–40
Coronary lesions	−100 to +75	4 wks.–6 mos.	−100 to +75	6 mos.–2 yrs.	75
Aneurysm, aortic	−100 to +45	3 wks.–6 mos.	−100 to +75	6 mos.–2 yrs.	40–60
Early symptomatic neurorecurrence N. II, VII, VIII	[illegible] to 25	2 wks.	0 to 100	6 wks.–3 mos.	N. II, 50, N. VII, 95, N. VIII, 25.
Meningeal neurosyphilis	25 to 50	3–4 wks.	[illegible] to 100	15 mos.–[illegible] yrs.	80
Vascular neurosyphilis	20 to 50	6 [illegible]–6 mos.	−100 to +80	6 mos.–2 yrs.	[illegible]
[illegible] syphilis	25 to 50	6 wks.–3 mos.	60 to 80	18 mos.–6 yrs.	74
Tabes, fully developed	25	6 wks.–6 mos.	50 to 75	1–3 yrs.	45
[illegible]	0 to 10	6 wks.–6 mos.	25 to 50	2–3 yrs.	25
Simple primary optic atrophy	−75 to +65	6 wks.–6 mos.	−100 to −25	1–3 yrs.	50 ([illegible])
Early paresis	25 to 50*	3–4 mos.	−100 to +100	1–6 yrs.	[illegible]
Late paresis	0–25*	3–4 mos.	−100 to +75	1–10 yrs.	30–40

[illegible]
*Includes fever and tryparsamide.

per cent" in the case of the chancre allows for the therapeutic shock (Herxheimer) in the first twenty-four hours specified.

The Meaning and Possibilities of Relapse.—Syphilis is the relapsing disease par excellence and every reflection on its prognosis must be colored by this qualification. In fact, the physician increases his effectiveness in no small degree in proportion to the extent that he has absorbed this maxim and put it into practice. He should school himself to a constant and systematic alertness a habit of search for signs of relapse which makes it impossible to dismiss a patient under observation with verbal assurances based merely on a negative blood serological test, for example. Search for evidence of relapse should be as objective and painstaking as search for the diagnostic signs of the disease in the first place. Relapse is serious for the social order early in the disease and often especially serious for the patient because it finds him deprived by the quick destruction of most of his organisms of the resistance-

building forces provoked by their presence in his tissues. The patient's contacts thus become the victims of his recurrent infectiousness, while he himself through a strategically situated focal relapse in an unprotected structure like the nervous system may be crippled for life. Inadequate and poorly systematized or unwisely directed treatment of the disease forms very properly the material for a special discussion (Chapter XIII). On the other hand the physician who encounters a relapse at some point where he least expects it or where he believes it most completely guarded against, should not lose faith in treatment or assume an uncritically pessimistic outlook toward the control of the disease. Relapse is an inevitability in syphilis in a certain proportion of patients in every phase and stage, and no device, ancient or modern, can completely prevail against it.

The Influence of Modern Treatment on Prognosis.—Symptomatic results have been drawn on time and again by conservatives not only for their own worth but to give credit to the inference that letting the disease alone or at best interfering in only the slightest degree, as with mercury pills and iodide, for example, with its normal course leads to a high proportion of long lives free from significant complications. While there are in all phases of the disease and under all methods of treatment instances in which a single arsphenamine injection healed a chancre and "cured" the patient, or a few pills and iodide given in the twenties left a man robust in the eighties, these striking examples that rise so readily to the lips of the "Old Guard" cannot be accepted as establishing the case for an utter disregard of prolonged and intensive treatment *as a guarantee of safety*.

It is very interesting to note in the literature the decline of reminiscent articles dealing with the benign course of syphilis in the prearsphenamine era since 1921, at which time, both in this country and abroad, the results of the first decade of arsphenamine therapy were in process of collection and publication. Extremely interesting reviews of the course of syphilis under régimes of minimal treatment, or no treatment at all, have been made by Blaschkow, by Lesser and by Bruusgaard (1929). Fournier and Neisser at the height of the mercurial era had, with an almost exact correspondence of their percentage figures, shown that among tabetics and paralytics approximately 55 per cent had received no treatment and 40 per cent very little treatment, while only approximately 5 per cent had received repeated courses of mercury. A famous statistical series of Mattauschek and Pilcz, who studied syphilis among Austrian army officers, included 1188 patients in whom, for example, the incidence of paresis was 23 per cent in the untreated and those receiving only one course of mercury, as compared with 5.83 per cent in those receiving repeated courses. Similar figures applied to other aspects of neurosyphilis in their group. Turning more specifically to the comparisons between the mercurial and the arsphenamine era, Des Brisay and Stokes, and Barner and Stokes undertook statistical studies of the prognosis of syphilis from the material of the Section of Dermatology of the Mayo Clinic in an attempt to satisfy themselves on this point. The controls in such an investigation are exceedingly difficult, but even allowing for the defects thus introduced, Des Brisay and Stokes found from a study of about 500 cases that untreated syphilis runs a definitely less favorable course than treated syphilis. Fewer than 1 per cent of 208 untreated cases had attained serological and symptomatic cure. After treatment by mouth 6 per cent were totally arrested and 10 per cent had attained serological negativity on blood and spinal fluid. Of 178 who had had modern but none the less entirely inadequate and desultory treatment, nearly 18 per cent were serologically negative on the blood as against 9 per cent of untreated cases, and 10.5 per cent of patients treated by mouth. In syphilis treated by modern methods even improperly applied, considerably less than half as much cardiovascular, visceral, osseous and cutaneous syphilis developed as in untreated and mouth-treated syphilis. A patient with syphilis treated by mouth *evidently relies quite largely on his physiologic defence*. It would seem, then, from their results, that even a little treatment is better than none.

Bruusgaard's statistics (1929), based on the after-histories of the cases of early syphilis that attended the clinic of Caesar Boeck, Oslo, during the twenty

years from 1891 to 1910 and who had received no specific treatment whatever have been widely quoted as indicating that in the majority of instances syphilis was cured spontaneously In fact Sowder (1940) believed from his reanalysis of Brusgaard's data, that they tended to exaggerate rather than to minimize the seriousness of syphilis Harrison (1940) on the contrary felt that there were serious limitations to these findings as an indication of what happens when syphilis is not treated with any specific remedy Vonderlehr and Usilton (1938) found that treatment decreases the probability of a disas-

Fig 67.

TREATMENT IN EARLY STAGES OF INFECTION IN CASES OF CARDIOVASCULAR SYPHILIS, GENERAL PARESIS, TABOPARESIS AND TABES DORSALIS

Total cases investigated and those described having been treated properly in early stages of infection.

Authors	Cardiovascular	Central Nervous System: G P I. and Taboparesis	Central Nervous System: Tabes	Total Investigated	Total Classed as Properly Treated in Early Stages.
A. Møller Dekam (1928)	100			100	1
D C. Smith and R. D Kimbrough (1928)	56			56	0
F E. Weatherby (1929)		155	81	166	2
J F Madden (1930)	40	157	136	333	2
P A. O'Leary and J R. Regan (1932)		77	219	296	3
J Strandberg (1937)		234	75	309	6
W P Thompson, W J Cowan and P D White (1930)	20			20	2
	216	623	465	1,308	16

Figures given in this table do not include all cases reported on by authors quoted. Meningovascular cases excluded on account of difficulty of distinguishing in any brief form early from late cases. Harrison, L. W *Brit J Ven. Dis* 16.1 1940.

trous outcome in syphilis. Symptomatic central nervous system disease decreases from seventeen in one hundred untreated syphilitic patients to two in one hundred under standard treatment during early syphilis. No patients with cardiovascular syphilis were detected among those well treated and reexamined ten to twenty years after infection (Fig 68 and Kemp and Cochems, 1937) Excellent results (85 per cent cures") obtained with standard treatment in early syphilis reported from patients examined in the three to ten-year observation period were maintained by those patients so treated

and reexamined ten to twenty years after infection The careful study of Padget (1941) based on 551 patients from the Johns Hopkins Clinic, completely reexamined at least five years after the termination of two years of treatment is a monument dedicated to the effectiveness of early adequate treatment and the permanence of results obtained by such therapy Padget found that continuous was superior to intermittent and irregular treatment So many of the patients did so well on little treatment that attention is called to the fact that adequate treatment for all of a large group of patients with early syphilis inevitably results in over-treatment for many A little treatment (7–9 arsenical) in the first three months of treatment is as effective as

Fig. 69

THE OUTCOME IN TREATED EARLY SYPHILIS COMPARED WITH THE OUTCOME IN UNTREATED EARLY SYPHILIS (ANALYSIS BASED ON LIVING PATIENTS ONLY)

Status of patient at time of final examination	Untreated cases[1]		Less than standard treatment		Standard treatment	
	5–10 years	10–20 years	5–10 years	10–20 years	5–10 years	10–20 years
	Per cent	*Per cent*	*Per cent*	*Per cent*	*Per cent*	*Per cent*
Neurosyphilis						
Symptomatic	5.7	16.9	4.1	10.3	0.6	1.6
Asymptomatic	12.7	6.1	4.6	3.7	2.6	1.6
Cardiovascular						
Definite	1.9	3.4	1.4	5.8	1.2	
Possible			.6	2.1	.2	4.9
Skin, mucosal or bone	32.0	29.5	2.4	1.6	.4	
Visceral	1	1		.3		
Ocular	1			.3		
Symptom free						
Positive blood	31.0	9.2	19.5	17.3	7.7	6.6
Negative blood	10.3	34.6	67.4	59.0	87.3	85.3
Total	100.0	100.0	100.0	100.0	100.0	100.0
Number of cases	510	328	848	191	904	61

[1] Bruusgaard whites and southern Negroes weighted by proportion of each race in U S A.

[2] Cases in 5 cooperating clinics in U S. A.—Cases receiving less than 20 doses of arsenical with heavy metal plus irregularly treated cases receiving 20 or more doses of arsenical with heavy metal.

[3] Cases in 5 cooperating clinics in U S A.—Continuously and intermittently treated cases receiving 20 or more doses of arsenical with heavy metal.

From Vonderlehr and Usilton, "The Chance of Acquiring Syphilis and the Frequency of its Disastrous Outcome *Ven. Dis. Inf* Nov 1938

twice as much treatment scattered over the first two years For practical purposes, it was shown that a patient who has done well for five years following the termination of treatment for early syphilis, and at that time presents no evidences of the disease to be found on complete examination, may be discharged from further observation Padget further reemphasized the ominous prognostic significance of early or immediate clinical relapse. Vonderlehr and Usilton (1938) have in tabular form (Fig 69) summarized succinctly the findings from the Cooperative Clinical Group's large material

The Arsphenamines and Neurosyphilis.—It has been insistently suggested that the use of arsphenamine predisposes to neurosyphilis and that methods which rely more upon the patient's physiologic defence such as medication by

mouth yield in the aggregate a milder course and fewer late complications than the hammerings of modern procedure. The best evidence now available indicates that such is not the case.

The longstanding controversy began with Finger who, in 1911, reported 9 per cent of neurorecurrences in his first 500 arsphenamine-treated cases as contrasted with 0.25 per cent in 2000 cases treated with mercury and iodide. This question was answered in the negative by Des Brisay and Stokes when they found that patients untreated, mouth-treated and inadequately treated by modern methods all presented approximately the same incidence of neurosyphilis, namely between 42 and 50 per cent. Guy (1930) has critically reexamined this question. From his citations it appears that neurosyphilis unquestionably became more frequent after the introduction of arsphenamine but that the patients were in general inadequately treated, as in Pette's series from Nonne's clinic. Laster reached the same conclusion from the material of Strumpell's clinic in the years between 1900 and 1922. From their clinical study of 400 cases of neurosyphilis O'Leary and Ropa (1934) could find no substantiation of the idea that arsphenamine predisposes to, or induces the development of neurosyphilis. Mattauschek, in 1924, reported an increase in cerebrospinal syphilis and a stationary curve for dementia paralytica. Marburg showed a shortening of the incubation period in the arsenical-treated group. Hyder found the average incubation time for neurosyphilis among a group infected prior to the introduction of arsphenamine to average fifteen years and a group infected during the arsphenamine era to be seven years. In a well-documented study Kemp and Menninger (1936) found that early inadequate treatment does not increase the incidence of neurosyphilis; with no treatment, neurosyphilis comprises 34.6 per cent of cases, and with early inadequate treatment it comprises 43.4 per cent of cases. They found, however, that the incubation period of clinical neurosyphilis is reduced approximately five years in a group of inadequately treated patients as compared with a group receiving no treatment, i.e., from 19.2 to 13.1 years in males and from 14.9 to 8.7 years in females.

The point to be emphasized in judging the influence of arsphenamine on the prognosis of syphilis with respect to neurosyphilitic involvement is that practically most of the treatment discussed by the foregoing authors ranks as entirely inadequate when judged by present-day standards. The value and efficiency of modern treatment methods in controlling and preventing the development of asymptomatic and late forms of neurosyphilis is now quite thoroughly established and will be discussed in Chapter XX under the Treatment of Neurosyphilis. Merely as an illustration, Moore and Keidel produced the first convincing American evidence that effective combined arsphenamine and mercurial treatment reduces the proportion of patients destined for late neurosyphilitic complication from 26 per cent to the unprecedentedly low proportion of 3 to 5 per cent, by properly directed measures. Such a proportion is so much lower than any accepted statistics of the incidence of neurosyphilis in general, that the improvement in outlook must be accepted as exonerating modern treatment methods from any charge of perverted effect upon the nervous system.

Certain general evidence pointing to a decline in neurosyphilis in the arsphenamine era is appropriate as a defence of the arsphenamines against the charge of inducing neurosyphilitic complications. This material is reviewed by Guy and by Stower, both of whom reach the same conclusion, based upon well-established American figures for dementia paralytica and tabes, that there is a slight but definite decrease in an almost stationary rate and a definite decrease in mortality from these sources. Colonel Harrison has cited likewise convincing figures from British experience (1940).

THE MEANING AND DETERMINATION OF "CURE"

A Definition of "Cure."—Throughout this text the word "cure" has been thrown into quotation marks with the definite purpose of directing attention to it as an expression or verbal form rather than a completely established fact.

The effective definition by the physician of the problem of "cure" and of the methods which must be adopted to work toward it often makes all the difference between a loyal and distrustful patient, and between recovery and failure.

It is well to distinguish, in talking with patients, between clinical and pathologic or radical "cure." The former is defined as a complete relief from symptoms and signs of the disease and ultimate noninfectiousness, with free-

Fig. 70

PRINCIPLES OF PROGNOSIS IN SYPHILIS

I. General Considerations

1 Prognosis is influenced by the type of infection (symptomatic or asymptomatic) infecting organism, race ge and sex of the patient, pregnancy intercurrent infection and disease, and treatment (type, amount)
2. Infection may be asymptomatic throughout its entire course (33–35 per cent, Morgan, 1939) or long latency may precede serious late lesions.
3. The Negro is disposed to develop cardiovascular syphilis, the Whit neurosyphilis.
4. Syphilis may be more serious in the very young and the old.
5. Syphilis is pt t be milder in women and especially in the multipara.
6. A good early reaction (florid secondaries) may protect gainst neurosyphilis, "law of inverse proportions.
7 The serologic reaction is no guide to prognosis.
8. A patient with syphili runs risk in ddition t those of his disease, of predisposition to other diseases (g cancer) and of reactions t treatment.

II. Prognosis of Untreated Syphilis

1 Early Syphilis.—Syphilis shows spontaneous tendency t recovery and disables or kills only a minority of those infected. It may be cured spontaneously
( ) Bruusgaard (1929) showed that 27 9 per cent of patients are spontaneously cured. 22 6 per cent will die of other causes.
14.1 per cent will have only serologic evidence of syphilis.
12 8 per cent will have benign lat syphilis.
12 8 per cent ill have cardiovascular syphilis.
9 5 per cent ill have neurosyphilis. That is t say: One-third of untreated early syphilitics will develop benign or dangerous lat lesion, but two-thirds will pass through lif unharmed.
(b) Sowder (1940) Bruusgaard' results tend to exaggerate the seriousness of the disease rather than t minimize it
(c) Harrison (1940) There are serious limitations t the value of Bruusgaard' data as indication of the prognosis of untreated early syphilis.

II. Prognosis of Treated Syphilis

1 Adequate treatment of early syphilis cures and thus prevents late complications.
( ) W th continuous treatment, begun in the seronegative phase, cure in early syphilis may be obtained in 80 4 per cent of cases. These good results are lasting (Padget, 1940; Vonderlehr and Usilton, 1938) If treatment is delayed to the seropositive primary phase the satisfactory outcome is 64.5 per cent and for secondary syphilis, 81.5 per cent. (Stokes, Usilton et al (CCG) 1934)
(b) Clinical relapse is of grave prognostic import. Seropositive primary has the highest incidence of neurosyphilis and relapse The more arsphenamine, the less relapse (Stokes, 1936 Padget, 1940)
( ) Collected data from the literature show that patients with cardiovascular syphilis, paresis, taboparesis, and tabes dorsalis have rarely received proper treatment in early syphilis (16 of 1208 cases, Harrison, 1940, cf Vonderlehr and Usilton, 1938) Series of well-treated early syphilis result in little or no late syphilis (Padget, 1940)

Fig. 10.—*Continued*

II. Prognosis of Untreated Syphilis	II. Prognosis of Treated Syphilis
(*d*) *The spontaneous involution or curability of syphilis* cannot be depended upon to control infectiousness even if the public health aspects were controllable by quarantine	(*d*) Inadequate treatment of early syphilis predisposes to relapse shortens the incubation period of neurosyphilis, but does not increase the incidence of it. (Kemp and Menninger 1936)
2. **Latent Syphilis** untreated does not always terminate disastrously Cooperative Clinical Group (1934): About 33 per cent satisfactory outcome (freedom from manifestations of syphilis together with spontaneous serologic reversal) Twenty to thirty per cent will show progression or relapse (Clinical relapse especially prone to occur in latent congenital syphilis, Smith, 1933).	2. **Latent Syphilis.**—Treatment yields an ultimate satisfactory outcome in approximately 85 per cent of patients (CCG, 1934).
3. **Late Syphilis** is unpredictable because of the possibility of unrecognizable structural damage There is equilibrium as well as progression element in late latency and late syphilis.	3 **Late Syphilis.**—Treatment of late syphilis does not cure but prolongs life arrest progression and affords symptomatic relief (Grant, 1933; Padget and Moore 1933 CCG, 1930, 1938; Harrison, 1940; Kierland, O'Leary and Vandoren, 1942) Prognosis is an individual matter and depends on type of lesion present, type of treatment and tolerance of treatment. The outlook of patient with fully developed late syphilis (neuro or cardiovascular) has been improved by modern methods of treatment (Fever et)
4 **Untreated Syphilis and Pregnancy.**—Pregnancy may suppress early manifestations. Repeated pregnancies have protective effect. Cooperative Clinical Group (1934) Pregnancy is auxiliary treatment, especially for the colored woman. The pregnant syphilitic woman has less relapses and less clinical progression than the non-pregnant woman. The untreated pregnant syphilitic woman has only one chance in six of bearing live, healthy infant as compared with the normal woman three chances in four	4 **Treated Syphilis and Pregnancy.**—Adequate treatment of syphilis in the pregnant woman assures a living nonsyphilitic child in 91 per cent of the cases (CCG 1934). Treatment of syphilis in the pregnant syphilitic prevents progression and relapse
5. **Life Expectancy of Untreated Syphilis.**—Life expectancy of males with acquired syphilis is shortened from that of the general population from ages 30 to 60 by 17 per cent in the white male and 30 per cent in the colored male (Usilton and Miner 1937).	5. **Massive-dose arsenotherapy** is still experimental, but tentative evaluation of various reports indicates that satisfactory outcome in early syphilis may be expected in about 85 to 95 per cent of the cases (equal to that of routine therapy). (Hyman, 1941 Reynolds, Mohr and Moore, 1942) This treatment is encouraging in late syphilis (Kaplan, 1942) and in congenital and acquired syphilis in children (Levin, Hoffman and Koransky 1942).

dom throughout life from complications and recurrence under proper observation and control Pathologic or radical cure is defined as the complete extirpation of the infection the destruction of every one of the invading spirochetes, so that treatment may be dropped and the patient comport himself as though he had never had the disease. Clinical cure, taking syphilis in all aspects, and year in and year out, can be brought about in 80 to 100 per cent of patients who will cooperate in treatment and observation Pathologic or radical "cure" is still on a basis of theory rather than finally established fact.

"Cure" *versus* Arrest.— Cure in anything approximating the strict sense is discussable only for early syphilis Patients who have developed the late manifestations of the disease are usually the better for an explanation of the distinction between "cure" and symptomatic arrest. In a sense clinical "cure" is arrest, but for the patient who has sustained residual damage, arrest can be made clearer by pointing out to him the fact that restoration to normal cannot be expected where there has been permanent destruction of vital tissue by the disease.

Serological and Symptomatic "Cure. —*The former term means, of course,* permanent blood serological negativity with a permanently negative spinal fluid to the four tests. It goes without saying that this condition in the light of previous discussion is by no means equivalent to clinical "cure. Progression of the infection under a mask of complete serological negativity is in fact, especially frequent in the gravest aspects of the disease such as cardiovascular and neurosyphilis The patient determined to know the results of his "test" will more than once need to have this situation explained to him. Symptomatic "cure" means nothing more than relief from the presenting symptoms It is the *beau ideal* of snapshot and opportunistic syphilology and the *bête noir* of the conscientious syphilotherapist. In old age it has its place and it may be offered to the "wreck" whose hope of better things has gone the road of negligence or mismanagement but it has little place in the syphilotherapy of the active years of life In fact, it is a modern axiom that treatment of the syphilitic patient should invariably be carried beyond the point of symptomatic "cure" for in no other way can even a semblance of permanence be expected.

"Cure" in Early Syphilis.—Unfortunately upon the issue of individual cure in early syphilis, it is impossible to speak with absolute definiteness and assurance. Without question hope and wishful thinking will need constant and determined differentiation from certainty in this field for perhaps another 25 years. In two figures (71 and 72) we have attempted to summarize first a classification of evidence and alleged evidence relative to the curability of syphilis in its present-day status and secondly what might be used as a guide to the ritual of active and presumptive criteria and tests which should underlie the assertion that a given patient is "cured" It will be noted that the clinical criteria begin with statements regarding standards of treatment which the most critical of recent observers must must be incorporated into any estimate of the status of a given case with reference to "cure." The details of the treatment method comprehended under these heads are discussed in Chapter XIV Points 6 and 7 on the clinical side, emphasize the necessity for physical examination, for which no roentgenological or serological procedure can ever be a substitute. Point 8 recognizes the completeness of asymptomatic latency in women. Point 9 is based on the current belief discussed later that two negative examinations of the spinal fluid a year or two apart, after treatment has been completely suspended justify belief that the central nervous system

Fig. 71

A CLASSIFICATION OF "EVIDENCE" RELATIVE TO THE "CURABILITY" OF SYPHILIS

Pro.	Con.
1. Undoubted curability in animals.	1. Lifelong infection if untreated in animals.
2. Reduction in the incidence of the disease in populations.	2. Examples in man of asymptomatic course and prolonged latency (up to fifty to sixty years)
3. Reduction of incidence of certain complications (paresis)	3. No absolutely valid, single or combined proof applicable in life.
4. Results of blood serological surveys and recheck of treated cases.	4. Known clinical progress in spite of serological negativity in blood and spinal fluid. a. Clinical activity in spite of provocative negativity
5. Results of complete reexaminations, physical, serological, neurological (including CSF) cardiovascular of treated cases.	5. Too short duration of observed cases.
6. Occasional negative autopsies of treated cases (Fig. 436)	6. Too few autopsy proofs based on microscopical study of adequately treated syphilis in man
7. Existence of spontaneous cures.	7. Evidence that therapeutic and prophylactic agents are bacteriostatic not bactericidal (Kolle and Evers with bismuth. Turbelle on prophylactics. Eagle 1938–1939)
8. Existence of immunity to reinfection independent of cure. Gives hope of cure which does not require reinfection to prove it.	8. Small proportion of spontaneous cures.
9. The apparent ready response (symptomatic) to treatment	9. Kolle's concept of the symptomatic carrier
10. Evidence provided by reinfection (proved)	10. Uncertain status of reinfection as proof of cure in the light of newer knowledge of superinfection.
11. Assertion and hope	11. Ubiquity and frequency of various forms of relapse and their confusion with reinfection. (See Reinfection after intensive arsenotherapy.)
	12. The contentions of Warthin based on spirochetal findings postmortem.
	13. Time still too short to determine cure (not less than fifty years required)
	14. Increasing difficulty of demonstrating serological negativity with increasingly sensitive technics.
	15. Birth of syphilitic children to completely asymptomatic mothers.
	16. Uncertainty of tissue transplant as proof of cure (Chesney and Kemp, Haleeby and Greenbaum, Worms and Schultz, Lake and Bryant) (*Establishment of the lymphatic reservoir conception in man.*)

is permanently free from involvement, a statement to which there are inevitable exceptions. Point 10 setting reinfection after a number of years as clinical evidence of "cure," will be subject to criticism in subsequent paragraphs. The crux of the whole problem and the concession that must be made to the

Fig 7d.

ITEMS IN THE PROOF ACTUAL OR PRESUMPTIVE, OF "CURE" IN SYPHILIS

Clinical	Laboratory
1 Early beginning of treatment (seronegative primary or first few weeks of secondary period)	1 No suggestion of temporary positive in an initial seronegative case.
2 Vigorous nd prolonged treatment (Moore and Kemp, Hoffmann, Sezary Chargin and Stone Harrison)	2 A normal rat of reduction of positive blood serological tests t negative (not too rapid) Preferably controlled by quantitative procedure.
3. Effective se of arsphenamine (Stokes, Cole et al)	3 No clears slowly and weak positives in any subsequent tests.
4. Continuous treatment (Moore nd Kemp, Stokes and Becker Stokes, Miller and Beerman, Am. Coop. Clinical Studies)	4 N serological relapses in series of tests over period of years.
5. Absence of all subjective symptoms.	5 T test procedures used in each case (Wassermann and precipit tion, including "presumptive type")
6 Absence of objective physically detectable lesions, especially heart and nervous system.	6. Negative provocative and serological test series t outset of new courses (see p 103) The negative provocative test is not reliable evidence of cure.
7 Negative cardiovascular stripe t roentgen-ray examination and fluoroscopy	7 The spinal fluid cell counts and total protein absolutely normal in blood-free specimens.
8. In women, the nonappearance of syphilis in children unprotected by treatment	8. Negative lymph node and tissue (chancre scar) inoculations into animals (followed t or more generations)
9. T or more spinal fluid examinations negative interval one year or over	9 Autopsy complete, controlled by microscopical and animal inoculation studies.
10. Occurrence of reinfection after the period of relapse and with fully satisfied criteria (Hoffmann)	
11 Repeatedly negative complet physical reexaminations over a period of as many years as possible, up t ld Thus t nclude ey and ear	

THE RADICAL OR COMPLETE CURABILITY OF SYPHILIS IN MAN REMAINS TO BE PROVED THE CONTROL OF THE DISEASE BY PREVENTION OF INFECTION IS POSSIBLE

insoluble elements in the riddle of syphilis in man are the lifelong periodical examination and the necessity for an autopsy of almost unheard-of completeness as a demonstration of "cure." The patient clamoring for radical assurances usually subsides into silence when the practical valuelessness of the indispensable autopsy criterion for his peace of mind is pointed out.

The intensely human and inevitably fallible element in the determination of cure are nowhere better illustrated than in the evaluation of the older standard treatment and the newer foreshortened intensive therapy of early syphilis. There is a curious and interesting uniformity to be pointed out in the percentages of good result not alone in syphilis by a variety of methods of treatment, but even in the treatment of other diseases by newer methods — in the case of gonorrhea. It seems that expectancy of cure by modern chemotherapy has a tendency to approximate 80 to 90 per cent of patients treated by empirically or experimentally determined standards. This suggests that a residue of 10 to 20 per cent of human beings infected with these diseases will, for various reasons, not as yet clearly understood, fail of cure despite the employment of the most intensive and effective methods. It is at this "inveterate residue" against which, in syphilis at least, much of the prolongation and intensification of therapy is being directed. It is clearly recognized that far more moderate standards could secure an 80 per cent "satisfactory" result. In this zone of the inveterate residue the stiffened criteria of cure must be sedulously applied lest wishful thinking and the inevitable human desire to prove the value of an investigated or favored method, warp the judgment of the investigator. These remarks apply specifically to the use of such criteria as reinfection in determining the curability of the disease. The differentiation of relapse and reinfection which is, of course, essential to the value of reinfection as a criterion of cure can be loosely carried through, with strong and visible desire to increase the number of reinfections in order to prove more cures. (Schoch) The conservative reaction of Leifer, Chargin, and Hyman, and of Elliott, Baehr, Shaffer, Usher and Lough and Thomas and Wexler is to be commended. They have refused to allow the slightest trace of wishful thinking to enter into their estimate of the effectiveness of the 5-day drip and multiple injection technics they employ by calling even plausible (though not "air-tight") reinfections anything but relapse.

The group disposed to relax reinfection criteria (Moore, editorial 1945) points out, however very properly that changes induced in the immunologic responses of syphilitic disease by rapid intensive treatment, may prevent the development of immunity and hence increase the probability and possibility of reinfection. The most that can be said at this moment is that the experienced investigator knowing the many factors involved, and knowing the inevitable human tendency to bend evidence towards the proof of a desired conclusion, will avoid temperamental reactions, wishful thinking, belief and hopes in his appraisal of the cold evidence for cure. Reinfection, especially in the light of what is known experimentally about superinfection, should still be examined most critically and available evidence should be classified according to grade of presumption it provides, whether or not we are "convinced of (her) promiscuity!"

The classification of evidence relative to the curability of syphilis at once discloses (Figs. 71–72), by the deadly parallel column method, the slenderness of the cord by which our hope seeks to mount to its fulfillment. On the clinical side the undoubted curability of syphilis in animals, the hope extended by the work of Chesney that reinfection is not indispensable to proof of cure and the results of complete examination of patients up to as long as twenty years after infection provide the chief substantial element. Figure 436 contains a summary of completely negative autopsied, treated case, but the number of such cases is all too few to carry much weight as evidence and the difficulties and rapid changes taking place in the technic of tissue examination, particularly under the studies of Warthin, have invalidated at least a part of such evidence as already exists. Here again must be quoted the highly significant statement of this lifelong *Spirochaetenforscher* made before the British Medical Association in 1929 that he has never seen a completely conducted autopsy which failed to reveal evidence of latent syphilis in syphilitic persons, or substantiated any claim to "cure. Warthin conceded, however that the five-year treatment ideal had not yet passed in review before his autopsy methods.

It should be emphasized at this point that much of the evidence adduced in favor of the curability of syphilis from the clinical side rests upon wholly inadequate clinical evidence. The tendency to rest upon a preconceived notion of the amount of treatment necessary for a cure in deciding whether or not a cure has actually been accomplished, may be a very serious one. It is equally impossible to depend upon any single test or group of tests applied at any given time for an absolute proof of cure. In discussing the mechanism and frequency of relapse, examples will be cited which will illustrate both these problems. The physician tends too readily to think in terms of courses and to rest his case with the inevitably arbitrary statement: "There, you've had enough. This relapsing test or finding must be false" instead of recognizing the ubiquity and, in certain cases, the inevitability of relapse

Serological Tests in "Cure"—The use of serological tests in determining the outcome of syphilis has been sufficiently discussed. It should only be

emphasized here that the instrument which will almost undoubtedly be invoked in the coming five to ten years, namely an ultrasensitive serological procedure for the detection of the faintest traces of positive tendency in the serum of the treated person, is a double-edged procedure which, as yet, at least, rests on an imperfectly developed interpretation of the actual meaning of the presence of syphilitic reagin in the blood with respect to activity arrest or "cure Clinically however it may be stated that no series of negatives in any form of serological test on blood or spinal fluid can carry absolute weight with respect to cure" in our present knowledge of the situation.

Tissue Transplantation in "Cure" Evaluation.—In the first edition of this text it was suggested that rabbit inoculation might be used to take advantage of the possible existence of lymph node reservoir in man t demonstrate the presence of *Spirochaeta pallida* or its absence, in supposedly cured cases. More recent work seems to make this method appear of doubtful reliability

Chesney nd Kemp pplied this method in 8 patients, obtaining negative results by lymph node inoculation after treatment and subsequent observation periods ranging from one to four and three-fourths years Saleeby and Greenbaum elaborated and extended the method, reporting on 89 patients with cute and chronic untreated syphilis from whom inguinal lymph nodes were removed and reporting that the condition of the rabbit, particularly ith respect to feeding, was vital in these experiments. In the 23 results which they were able to interpret from this series, it was found that the nodes of patients with untreated acute early syphilis always contained *Spirochaeta pallida* but that this was true in only about 43 per cent of patients with untreated chronic syphilis. Of sixteen skin transplants from patients in all stages of syphilis, two gave positive results; two leukoplakic transplants gave negative results. They concluded that human node transplants cannot be used as means of determining cure in syphilis since *Spirochaeta pallida* disappears from these nodes spontaneously in many untreated and uncured cases. If they are not invariably present in untreated cases, their absence in treated cases is of no value so far as criterion of cure is concerned. These uthors pointed out that the disappearance of the secondary eruption in syphilis does not always mean destruction *in situ* of all spirochetes causing that eruption. The finding of residual spirochetes in two instances out of sixteen skin transplant studies made, suggested to them the reason for the development of gummas in later li They found that persistently enlarged lymph nodes in patients with syphilis are no indication of the presence or absence of *Spirochaeta pallida* in such nodes. Zieler and Hämel in 7 patients adopted an immunological method of testing the possible presence of latent syphilitic infection in the rabbit inoculated from lymph node tissue. The method employed was the cross-inoculation technic of Kolle using the Truffi strain, and from the very high proportion of infections which they secured in their rabbits they concluded that they had not become carriers of latent syphilis by virtue of their inoculation with human lymph node tissue and that the patients were, therefore, in all probability cured. These results must, of course, be subject to Saleeby and Greenbaum criticism of lymph node transplant as procedure. Use of the chancre scar for determining the survival of residual infection has some interesting possibilities based upon the observations of Sandmann, Pasini, E Hoffmann and others

Tissue inoculation methods have the apparently inescapable drawback of requiring the cooperation of a laboratory for experimental syphilis which, unless established under centralized control and facilities, is practically not accessible to more than a handful of clinics in the entire world.

Reinfection as a Criterion of "Cure."—In view of what has just been said regarding a tendency to relax criteria of reinfection in order to meet certain special immunologic conditions perhaps prevailing under intensive treatment for early syphilis and thus increase the justified evidence for cure we feel it doubly desirable to re-state the three grades of strictness (Fig 73) by which the validity of reinfection may be judged That the indisputable group embodies the strictest criteria yet promulgated does not for a moment *ipso facto* invalidate either the criteria or the propriety of using them in appraising the status of an alleged reinfection. If reinfection is to be more freely diag-

Fig. 72.

CRITERIA OF REINFECTION ARRANGED IN THREE GRADES OF STRICTNESS[1]

Grade I Indisputable.	Grade II: Probable	Grade III Possible.
1 First infection proved by blood Wassermann reaction or darkfield.	1 Indisputable first infection.	1 Indisputable first infection.
2. Negative physical examination t years after treatment.		
3. Negative blood Wassermann for one year after treatment.	2. Clinically and serologically negative for one year after treatment.	
4 Negative spinal fluid at end of treatment.		
5. No relapse between the two infections.		
6. Definite exposure history for second infection.		
7 Infectious source for second infection		
8. Normal incubation period for second chancre (seven to forty days)		
9. Second chancre in different site and lymph drainage from first.	3. Second chancre in (a) different site (b) different lymph drainage from first.	2 Second chancre different site from first
10. No activity at site of first chancre.	4. No signs of activity at site of first chancre.	3. Second chancre characteristic appearance
11. Positive darkfield, second chancre.	5. Positive darkfield on second chancre.	4 Positive darkfield second chancre
12. Satellite adenopathy present, second chancre.	6. Satellite adenopathy present, second chancre	
13. Blood Wassermann reaction of second infection, negative at start, must change to positive.	7 If blood Wassermann reaction becomes positive under observation or—	
14 Secondary eruption must appear not less than t enty days after first chancre	8. If secondary eruption ppears at the proper interval, laxity ill be allowed in items 2, 3b, and 6.	
15. Treatment of first infection must approximate 20 arsphenamine injections and 20 bismuth or mercury injections		5. Second chancre must appear at an interval after antisyphilitic treatment
16 Time interval between first and second infection must be 2 years or more.		
17 Competent observation must be had in both infections.		

[1] From Stokes, Cole, Moore, O'Leary Parran and Wile Ven. Dis. Infor 12:55–68, February 20 1931

nosed with or without intent to prove more cures by intensive technics, the grade of proof is still a matter of critical interest and places the use of "probable" and possible classifications in the same category with the use of prolonged serologic negativity and absence of clinical signs in the general evaluation of "cure." Infallibility can only be claimed for a procedure and for cases which have satisfied the strictest conceivable requirements. Such cases, under the stimulus of this challenge, are increasing in number (Cannon, 1933 Klauder and Butterworth 1934 Tobias, 1934 Kopp and Solomon, 1930 Hahn 1941 Allison, 1942) and this tendency should be encouraged instead of derided by those who have something to prove

The question was critically reviewed on the basis of two groups of material in 1930, the first by Stokes, Schoch and Ireland from the material of the Syphilis Clinic of the University of Pennsylvania, nd the second from the material of the Cooperative Clinical Group for Retrospective Syph lis Investigation a presented by Stokes, Cole, Moore O'Leary Parran and Wile t the International Dermatological Congress in Copenhagen. It will suffice here, since the discussion of reinfection should technically accompany that of relapse, which it so much resembles and from which it is with such difficulty differentiated, that the criteria of reinfection be reviewed (Fig. 73). The conclusions dra from these two studies and involving comparison of our own experience, that of 40 infections occurring in the Cooperative Clinical Group and 237 reinfections collected from the literature by Halley and Wasserman, plus number of critical reviews, including those of Bernard, Hell, Hudelo and Rabut and others may be summarized as follows: the evidence collected tends to indicat that many reinfections are vitiated as clinical evidence by their occurrence within the time period after the first infection and ith the amount of treat ment for the first infection hich characterizes from 80 to 93 per cent of relapses. The weaknesses of existing material on reinfection with respect t historical detail, adenopathy scar and site of the chancre, examination of the spinal fluid and adequate physical examination, are very striking. On the basis of the criteria grouped as indisputable, probable and possible reinfections, it appears that there are no indisputable reinfections the evidence for which conforms to every requirement, about 116 conform t moderately rigid standard and 120 conform to an average standard which in our ow opinion is too lax to provide for the confusion elements of relapse morphology It is suggested that the highest ideal of syphilological reporting would be the presentation of cases of airtight reinfection.

THERE IS NO PROOF OF "CURE" EXCEPT OBSERVATION

Time and Observational Control.—"Observation throughout life," a previously widely held ideal for the cured syphilitic, has been subjected to modification by several critical analyses, including those of Stokes and Usilton and Vonderlehr and Usilton based on Cooperative Clinical Group data, and Padget (1940) based on the material at the Johns Hopkins Hospital Clinic The first-named authors stated their findings as follows

The possibility of unearthing significant data in period of observation up to ten years after the cessation of treatment is from 8 to 23 chances in 100. For ideal continuous and inter mittent treatment respectively it approximates 8 and 10 chances in hundred. Hence it seems that for those ho demand absolute assurance for those whose timidity makes repeated serologic and clinical examinations the only escape from syphilophobia; for those who have been given inadequat or desultory treatment in the first year of the infection, and for women who may or have become pregnant, indefinitely prolonged or repeated observation is necessary On the other hand, for those who can accept reasonable and in fact high probability of cure after strict adherence to an effective and especially to continuous treatment regimen in the first two years, and hose lives will be shadowed or disturbed by the exactions of observation, five years of probation after treatment ends is sufficient. I special situations such as definite relapsing tendencies, observable during treatment, or marked predisposition to serious types of nvolvement early in the disease special consideration may be necessary All patients should be told that cardiovascular examination should be performed by competent observer in the five- t ten-year period because of the yet unevaluated status of this group of complications, and

that in the case of women contemplating conception the status should be reviewed, and in all probability the pregnant woman who has once had syphilis, should be treated for the disease throughout each pregnancy. Thus, potential cardiovascular disease and the transmission of syphilis to the unborn child remain the two intrinsic justifications for prolonged and repeated observation after prompt and adequate treatment for early syphilis.

To this statement Vonderlehr and Usilton's observations added the important fact that no significant difference between the incidence of satisfactory results among 504 patients followed from three to ten years, appeared in comparison with a partly overlapping group of 61 patients who had been followed from ten to twenty years. Padget's material, which perhaps more closely approximates the cross section of the performance of a first-class clinic found that no distinction was required between 278 patients who were followed for five to ten years, and 273 patients who were followed for ten years or more. Not one of the 170 patients who had attained "cure" five years after treatment was suspended, was found to have manifested progression or relapse at re-examination ten or more years after the original treatment, irrespective of its type or amount. This statement is obviously of great significance to public health administrators, life insurance companies, and various Federal and state agencies which offer insurance and pension benefits.

A guide which we believe effective for the re-examination of treated syphilitics for the question of "cure" is that given in Chapter II (Figs. 12 and 13). It should be emphasized that cardiologic expertness and particularly the adequate interpretation of the fluoroscopic picture may be of differential importance.

It appears, then, that the really sovereign tests of "cure" are time and observation. When after five years, the patient who has satisfied the serological requirements of the older writers by a negative blood and spinal fluid slowly develops signs of syphilitic vascular disease one learns that there are no infallibilities in modern therapeutic syphilology.

CHAPTER VI

THE HEAVY METALS AND THE IODIDES

Principles of Action of the Heavy Metals Reviewed.—It appears that the arsphenamines occupy one extreme of a mechanism combining both spirillicidal and resistance-building properties, with mercury at the other extreme and bismuth as an intermediate all three being united presumably by an underlying chemotherapeutic mechanism involving responses in the reticulo-endothelial system combinations of tissue protein with the active drugs to form spirillicidal agents and linkage with the glutathione oxidation mechanism of the living cell by which these parasitotropic substances act or by a direct spirillicidal action (Eagle 1938) It has long been evident that storage and rate of elimination in their reciprocal relations have an immense influence on the chemotherapeutic efficiency of the entire series of antisyphilitic drugs. As Hanzlik has stated in discussion, the amounts of mercury for example retained in the body to exert their effect upon the infection must be of the order of hundreds of thousands if not millionths of 1 per cent. The scientific evaluation of the action of heavy metals has been delayed for centuries to await the development of chemical methods for the detection of minute amounts present in large residues of organic material. Route vehicle salt and site are almost as vital to the clinical effects of the heavy metals in the treatment of syphilis as the metallic ions themselves.

Important Considerations in the Use of the Intramuscular Route for Heavy Metals.—Intramuscular medication, in spite of recent interest in oral bismuth therapy seems likely to replace almost entirely the simpler technics and a comprehension of the fundamental principles involved in this way of giving these drugs becomes doubly important. When a physician injects intramuscularly or subcutaneously a preparation containing a heavy metal, he brings into play eight factors in addition to the actual quantity of the metal introduced as follows

1 The solubility of the drug in the vehicle (Fig 74)

2 The solubility of both in tissue fluids

3 The local reaction aroused including reaction to the vehicle, reaction to the deposited or perhaps precipitated drug, and reaction to the drug in solution

4 Influence of the site of injection

5 Rate of absorption of the drug from the injection site

6 Accumulation of the drug at the injection site.

7 Late changes, produced by a series, as distinguished from a single injection, including possible altered absorptive capacity on the part of the tissue and altered elimination by the body (retardation in the case of Bi)

8 Toxicity effects which are irremediable if overdosage or overaccumulation has been allowed to occur

The eight named factors outrank, in the opinion of Hanzlik, for example even the quantity of the actual metallic principle introduced per injection. The ideal drug for various occasions will vary greatly with so commonplace a

consideration as the frequency with which the patient can come for treatment or the length of time he will continue it or the duration of the rest interval which circumstances will demand upon the completion of a course. Local

Fig. 71

COMPARATIVE RESUME OF BEHAVIOR OF HEAVY METALS WITH RESPECT TO SOLUBILITY

Soluble in water or propylene glycol	Water (or glucose) suspended (insoluble)	Oil-soluble	Oil-suspended (insoluble)
1. Simpler salts of heavy metals.	1. Only bismuth metal or salt practicable	1. Oil bismuth salts.	1. Heavy metals, simple and double salts.
2. More pain (local necrosis and inflammation)	2. Less than soluble salts.	2. Little or no pain.	2. Late local pain and induration.
3. Most rapid absorption.	3. Slow regular absorption.	3. Mild rapid absorption, regular and complete	3. Slow irregular absorption.
4. Frequent injection (daily to 3 times weekly)	4. Once weekly	4. Once or twice weekly	4. Infrequent injection (weekly)
5. Rapid action.	5. Fairly rapid action.	5. Moderately rapid action	5. Slow erratic action in some, good in others. Often powerful effects.
6. Transient effect	6. Moderately prolonged effect.	6. Moderately prolonged effect	6. Prolonged effect.
7. No encapsulation or sterile abscess tendency	7. Extensive deposition. Metals may encapsulate	7. Moderate deposition. No encapsulation.	7. Encapsulation occasional, tend to form soaps and deposit calcium. Foreign body reactions.
8. Toxicity high but controlled.	8. Toxicity low	8. Toxicity low	8. Toxicity unexpected and often high due to difficulty in control (accumulation, erratic absorption)
9. Rapid elimination.	9. Good but more prolonged elimination.	9. Rapid elimination.	9. Prolonged elimination
10. Little accumulation.	10. Marked accumulation in metals, less in salts.	10. Little accumulation.	10. Very cumulative.
11. Quick local and sharp transient excretory mechanism irritations.	11. No excessive irritation or toxicity	11. No excessive irritation or toxicity	11. Late chronic intoxications.
12. No embolism.	12. Emboli and infarct possible	12. Emboli possible	12. Emboli, local and systemic

reaction will determine the patient's willingness to continue treatment quite as much as it will the absorption of the drug and local reaction will be determined quite as much by the vehicle as by the drug itself

The Local Reaction.—Lomholt has suggested that a moderately pronounced local reaction *is an advantage in securing rapid and effective absorption* rather than the reverse and has protested the disposition of manufacturers to select preparations too exclusively on their nonreaction-producing qualities. It seems not improbable that some of the nonspecific action of intramuscularly injected heavy metals may be comparable to that of sulphur, turpentine and *so forth*, *in arousing the defence mechanism through nonspecific inflammatory* effect as well as through the action of the injected drug. In this way perhaps calomel, the famous local-reaction producer of the mercurial era, in spite of its tremendously slow absorption and cumulative effect, gained some of its reputation as a powerful antisyphilitic remedy. Local reaction is influenced not only by the vehicle, the water-soluble preparations producing the most reaction immediately, and the oil-soluble preparations late, but it is affected by the degree of subdivision of the suspended drug.

Lomholt showed, in the case of bismuth oxychloride, that the smaller the particles the more *rapid the absorption and the greater the pain produced, while the larger particles produced little* local effect. An optimum size of 3 to 5 μ proved a satisfactory compromise between good rate of absorption and minimal local pain production. This effect has also been observed with calomel and potassium bismuth tartrate in oil, English calomel having long been given preference, presumably because of its fine state of division, and certain lots of insoluble suspension sometimes giving rise to much more marked local reaction and even to abscess formation, while other lots *of the same drug identical in chemical composition are well tolerated.*

Distribution of the Drug *In Situ*.—The aqueous suspensions of insoluble preparations show a much wider distribution than the heavier oil suspensions of very finely divided powders. These latter, as Lomholt has noted, form *sharply localized deposits which often undergo rapid encapsulation.* **Massage becomes consequently a particularly important part of the technic of intramuscular injection, especially of insoluble preparations, for it tends to widen the area of absorption and prevent encapsulation and excessively severe local necrosis, with pain, breakdown or abscess formation.**

Grabast has specially studied the comparative reactions of intramuscularly injected preparations, including the arsphenamines and heavy metals. He emphasizes the fact that every intramuscular injection leaves a scar. Most very irritating preparations, such as the arsphenamine group, produce abscesses whose contents are very slowly absorbed, and mercurial and bismuth compounds producing such local reactions only in less degree. He rates mercury thiobenzoate, benzoate, and cyanide as producing the most rapidly absorbed tissue changes and sodium bismuth thioglycolate as a water-soluble and tissue-fluid-soluble preparation as producing the least local reaction of all. Whether in view of Lomholt's opinion just cited, this is an advantage or not would seem to deserve further study.

Absorption from Injection Site.—The absorption of heavy metals from *injection sites depends apparently upon solubility in tissue fluids rather than* on phagocytosis. Sproull and Lehman (1042) for example, found that intramuscular absorption at comparable hydrogen ion concentrations is a function of the chemical stability. They also found that in general absorption (after oral administration) is also a function of the stability of the preparation in the presence of chloride or phosphate. *In general it is accepted that the heavy* metal goes into an albuminoid combination, though this can hardly be invariably true if Lomholt's observation on the elimination of mercury salicylate as such is correct. The bismuth protein combination has been given a special name by Levaditi (bismoxyl) and is assumed to be a highly spirocheticidal substance of which only minute amounts *are necessary for physiologic action*

The Local Depot.—It is apparent from this summary that the local depot produced by the deep subcutaneous or intramuscular injection particularly of oil-suspended insoluble heavy-metal preparations and of arsenicals which produce a high degree of local necrosis, abscess formation and encapsulation becomes an extremely important element in their therapeutic effect. The sharp difference between intramuscular and subcutaneous deposit of the injected material is well illustrated by the findings of Von Oettingen, Todd and Sollmann, who *in a study of bismuth hydroxide found that 30* per cent of the injected material was unabsorbed after thirty days following intramuscular injection but even after seventy days following subcutaneous administration, 90 per cent of the injected bismuth could be recovered from the site of injection (*vide* Anwyl Davies, who recommends the deep subcutaneous use of bismuth) An additional peculiarity of oil-suspended preparations, likewise of considerable importance is their tendency to form calcium soaps at the site of injection followed occasionally by quite extensive calcification which is particularly confusing in the attempt to identify the presence of unabsorbed drugs by roentgen-ray

An additional consideration of import nce in intramuscular injection, from the investigative standpoint, is the striking difference in the rate of bsorption of heavy metals from deposits in different animals. According to Von Oettingen, Todd and Sollmann, the absorption of ter soluble bismuth citrate in rabbit is much slower than in cats, the ratio being as high as 1: 4 This, with the greater tolerance of the rabbit for bismuth, as demonstrated by Kambel, makes it appear that the rabbit is not particularly satisfactory animal for the study of heavy-metal effects in the treatment of syphilis

Muscle Use as Affecting Absorption.—Gruhzit has demonstrated with excellent microphotographs the greatly increased grade of absorption which takes place when the drug is injected into an active muscle. This is a sufficient reason for the preference of the gluteal muscles, constantly involved in walking and massaged by sitting in comparison with the infraspinatus beneath the scapula, for example which is sometimes used as a site in shoulder injections.

Shaking the Suspension as Affecting Absorption.—This has been investigated by Cole and associates who have pointed out that even with fairly vigorous shaking the dose of heavy metal delivered from the top of a bottle containing a hand-shaken suspension, even though beads were used in agitating the preparation, may be as little as one third of the normal or supposed amount. In the case of bismuth preparations the variation as a result of this factor was least with a bismuth subsalicylate cream The mechanical shaking method has given us much better results.

Absorption by Container—A gelatin capsule has been shown in one preparation to be responsible for the taking up or fixation of a good part of the mercury bichloride in the contained fat suspension.

The foregoing emphasis on the storage of heavy metals at the injection site must not be allowed to obscure the equally great importance of the internal storage of the drugs concerned in various organs of the body This will be taken up separately for bismuth and mercury

BISMUTH

General Considerations the Replacement of Mercury by Bismuth.—Just as the spirillicidal therapy of syphilis was transformed by the synthesis and

application of the arsphenamines, so the heavy-metal therapy of syphilis has sustained its miracle within the past two decades in the practical substitution of bismuth for mercury throughout the larger part of the syphilological field. This change, which seems comparable in the opinion of many observers to the introduction of the arsphenamines, is the product of two peculiarities of the new drug: first, its superiority in spirillicidal effect as compared with mercury, though still inferior to that of the arsphenamines; and secondly, its greatly lessened toxicity as compared with mercury. The latter consideration especially has removed from the minds of the majority of observers the objection to prolonged continuous treatment with the arsphenamines and heavy metals. These considerations easily outweigh the inconveniences and lack of flexibility, such as they are, of a single-route drug. Bismuth thus finds its place particularly easily in an era dominated by the intravenous administration of the arsphenamines.

Historical Considerations Concerning Bismuth.—Bismuth, in contrast with mercury, is indeed a therapeutic newcome. Its first therapeutic use was apparently by Odier in 1786, the first animal experimental work was carried through by Orfila in 1842, the phosphorus-like injuries to heart, kidneys and liver were studied by Lebedeff, the distribution of the drug in the tissues by Dubinsky in 1870, and bismuth was demonstrated microscopically in the epithelial cells of the mouth in the same year. Kunkel early demonstrated the point already mentioned regarding the marked *difference in behavior of the drug in different animals. While it is generally accepted that Balzer* in 1889 first introduced the treatment of syphilis with bismuth, Levaditi points out that Masucci had already employed the drug in secondary and tertiary manifestations and Reynolds had recommended it in syphilitic suppurative processes. The use of the highly toxic bismuth ammonium citrate was apparently responsible for Balzer's failure to popularize the use of bismuth in the treatment of syphilis and the drug suffered a prolonged obscurity until Sauton and Robert, in 1916, studied the action of the tartro-bismuthate on chicken spirillosis and, finding that the sodium salt exercises a bactericidal action on *Spirochaeta gallinarum*, suggested that it might be useful in the treatment of syphilis. Following Sauton's death in the War, Sazerac revived his studies and, with Levaditi, in 1921 announced that the tartro-bismuthate of potassium and sodium has a decided curative effect on experimental syphilis in rabbits. In the following year (1922) after tests on man, they stated that bismuth is comparable to the best antisyphilitic remedies and rated its effectiveness as greater than mercury though less than the more active arsenical drugs. This clinical testing of the preparation was then taken up more elaborately by Fournier and Guénot, who announced, following the treatment of 200 cases, that the *Spirochaeta pallida* disappeared rapidly and the Wassermann reaction became negative in primary and secondary cases although it was comparatively little altered in late syphilitic disease. Sazerac and Levaditi and Fournier and Guénot worked with the comparatively unsatisfactory insolubles, including the citrate, subgallate and tartro-bismuthate. It is an interesting commentary on the narrow escapes from glory that give the human touch to the scientific field, that Kolle and Ritz had worked with intravenous injections of colloidal bismuth in the treatment of *Spirochaeta cuniculi* infections in rabbits, in 1919, and found them to be ineffective.

The grave toxicity of bismuth by intravenous injection was first shown by Sazerac and Levaditi and substantiated by Klauder and by Sollmann and Seifter (1932). Klauder further showed the inactivity of bismuth by inunction. With these studies as a base, the investigative work and literature involving bismuth has grown to colossal proportions, completely dwarfing both in quantity and scientific value the entire tradition of mercury, both clinical and experimental. The world-wide dominance of the arsphenamines has not escaped the critical attack of bismuth enthusiasts and there were clinics, such as that of the Hôpital Cochin in Paris, in which not a single injection of an arsenical had been given for more than ten years after the advent of bismuth (Fournier, Schwartz).

Spirillicidal Action of Bismuth.—Depending on the dose type of preparation (soluble insoluble) and route of administration (injection or oral administration) various studies have shown that the rate of disappearance of spirochetes from the early lesions of syphilis in man varies from about twenty four hours to about eighteen days while neoarsphenamine causes spirochetes to disappear from similar lesions in less than twenty four hours to more than six days Pronounced though the spirocheticidal properties of the drug certainly are, it must be repeated that as shown by this comparison they are not great enough to justify the complete substitution of the drug for the arsphenamines in securing the immediate sterilization of the patient, for public health if for no other considerations.

The Mode of Action of Bismuth.—The mechanism of action of bismuth is not definitely settled. It has been suggested that it functions as a catalyst for spirochetolysis *in vivo* (Levaditi *et al.*, 1924–1934) that it is inactive *per se* but combines with tissue derivatives, influenced by glutathione to form actively spirocheticidal compounds ("Bismoxyl" Levaditi *et al* 1924–1937) that it merely inhibits the multiplication of spirochetes (spirochetastasis) (Kolle and Evers, 1926) and that it is directly spirocheticidal (Giemsa, 1922 Kadisch, 1926 Kolmer 1926 Eagle 1938–1939 Kolmer Kast and Rule 1940)

Kolle and Evers have maintained that the action of bismuth is not spirillicidal but that the drug acts rather as an inhibitor of spirochete reproduction.

This view is based upon Kolle demonstration of the inhibition of chancre development in rabbits by depots or plugs" of bismuth injected int the tissues of the ear So long as the "plug as allowed to remain in place no primary lesion developed, but as soon as it as removed by excision the development of the chancre followed at intervals of from two t four months, approximately the normal time Worms accomplished the same effect in rabbits with intravenous injections of bismuth preparation (Balbern)

Eagle s recent findings partially anticipated by Giemsa s observations with higher concentrations of Bismutyl, by Kadisch (1926) by Kolmer (1926) and confirmed by Kolmer and his coworkers, indicate that the probable mode of action of bismuth compounds is directly spirocheticidal. He found by an *in vitro* method that soluble bismuth salts are actively spirocheticidal in dilutions of 1–50 000 to 1–225 000 (as dilution of bismuth metal) These concentrations are nearly those found in body fluids after therapeutic doses Tissue extracts contrary to Levaditi do not enhance but actually reduce the spirocheticidal action. This action is not affected by the absence of molecular oxygen and is probably due to the bismuth compounds as such. It may however rest on an affinity for sulfhydryl groups in the spirochete (*cf* Levaditi, glutathione) Kolmer Kast and Rule agree there is no reasonable doubt that bismuth is directly spirocheticidal both *in vitro* and *in vivo* but consider it an open question whether or not the element slowly dissociates from deposits of the compounds as administered intramuscularly for these effects, or whether the compound first effects a union with the tissues from which organic bismuth complexes the metal is slowly dissociated with direct spirocheticidal activity

Collateral Effects of Bismuth.—Certain other effects of bismuth on the animal organism deserve note The metal is a very effective diuretic, the early induction of diuresis being similar but even more marked than in the case of mercury and limited to a less degree by subsequent toxic injury to that organ

which is of course less with bismuth A number of observations on the effect of bismuth upon the blood picture have been recorded and are somewhat conflicting probably depending on dosage and salt employed In contrast to the marked anemia-producing qualities of mercury bismuth may produce a temporary slight reduction in erythrocytes followed by a definite rise. According to Marcozzi and Neuber the absolute and relative characteristics of the leukocyte count are also slightly affected (*cf* Fishback and Fishback, 1937 polymorphonuclear increase in rabbits.) Ramsas, Brown, Saleeby and Schamberg have shown that the effect on renal and nitrogen eliminative capacity and metabolism is dependent on injury to the kidney Administration of bismuth in amounts such as are used in the treatment of patients with syphilis causes abnormal changes at the site of provisional ossification of growing long bones. A succession of courses of bismuth treatment gives rise to a series of cross striations radiologically more dense than the normal bone between them. As the bone grows the dense bands become further removed from the epiphyseal line and they become less distinct and eventually vanish Although these changes are evident only during the process of bone growth and represent abnormalities of bone growth, prolonged bismuth administration does not interfere with the rate of linear growth (Ruskin, Stadler and Jeans 1942)

Pharmacology of Bismuth.—Considerable advancement of our knowledge of the pharmacology of bismuth compounds is due to the prodigious effort of several American groups of pharmacologists and chemotherapeutists including Sollmann and Cole Hanzlik, Kolmer and their coworkers

Absorption.—Many of the general principles governing the absorption of heavy metals have been worked out or elaborated in the intensive chemical study of bismuth All bismuth preparations injected into the musculature produce necrobiotic and necrotic processes as has been stated. The injury is least marked with water and tissue-soluble preparations, is more distinct with water-soluble and tissue-insoluble preparations and is very marked with aqueous and oily suspensions of insoluble bismuth salts Suspensions of colloidal metallic bismuth seem to produce somewhat less injury than the suspensions of the insoluble salt but the regenerative process seems to extend over a very long period Tissue- and water-soluble preparations are the most rapidly absorbed followed in order by the water-soluble and tissue-insoluble preparations, the aqueous and oily suspensions of insoluble salts and finally the suspensions of colloidal metallic bismuth which show the slowest absorption *from the site of the injection Insoluble bismuth soap formation has* been confirmed by Aubrey for man, in the case of the hydroxide.

Systemic bsorption of bismuth compound in nimals is demonstrated by determining the toxic effects nd fatalities with large doses, by the rat of disappearance of bismuth compounds from sites of injections and by their appearance in the urine after administration by various routes—intramuscula or oral.

The study of bismuth absorption by the use of the -ray originally applied to mercury while recognised as practically valuable method in man is show t contain serious factors of error due in part to the deposition of calcium at the injection sit Some of the differences in published results are probably due t difference in the rate of bsorption which has been shown by Cole by Gruhzit, and by Montagne t be due t the difference in the rat of absorption from f tty tissue and active and inactive m scular sites. Sollmann and Henderson (1936) have shown in dogs, for example that thiobismol is bsorbed practically completely in tw hours. With sod um tartrat and presumably other compounds studied, the amount absorbed increased materially beyond three hours Bet een eighteen nd fifty-one hours, there is little further absorp-

tion, if any so that the data are treated together for this span. Increased dosage increased the amount of the metal absorbed, but the percentage absorbed did not appear to be materially affected by doubling or tripling the dose The preparations may be arranged in four groups, in descending order of median absorption: the highest is thiobismol the other watery solution range in the second and third groups, the oily solutions in the second, third, and fourth groups, and the oily suspensions in the fourth, or lowest, group. With few exceptions, this order corresponds to the order of clinical excretion.

Considerable controversy has appeared in the literature recently as to whether bismuth administered orally is absorbed. Early observers (Sazerac and Levaditi, 1921 Fournier and Guénot, 1921) believed bismuth ineffective orally Serefis (1931) revived this mode of administration by developing for oral use a complex (half-ne mixture of bismuth chloride and sodium citrate in glycerine (bismutrat) which he claimed is absorbed and is actively antisyphilitic. It has given equivocal clinical result (Thomas 1937) and rather variable but slight bismuth excretion. Rein and Sulzberger (1936) found it promising as a prophylactic in experimental syphilis but Kemp and Rosahn (1936) found it, as well as potassium bismuth tartrate without demonstrable curative effect when given orally Kolmer (1937) stated that potassium bismuth tartrate orally cured 42 per cent of the rabbits with acute syphilis treated. In 1931 he also found that sobisminol orally is absorbed sufficiently in repeated doses to effect biologic cure in syphilitic rabbits Stratton (1938) found the urinary excretion of bismuth in rabbits after the use of several oral bismuth preparations to be satisfactory for bismutrat and sobisminol, less so for potassium bismuth tartrate and none at all for bismodide Hanzlik and his associates (1937 1938) made quantitative studies of absorption of bismuth from the ligated stomachs and ligated loops of intestine of rabbits and white rats after injection of sobisminol solution. In limited series, approximately 50 per cent of the sobisminol solution placed into empty ligated intestine or stomach was found to be absorbed in from one to eight hours. A limit of bismuth absorption was reached at the end of twenty to twenty-four hours. The cause of this limit was due to relatively large quantities of bismuth in the intestinal or stomach wall.

They also found that absorption of sobisminol solution or mass in man, as evidenced by clinical studies, appears to be rapid and sufficient to maintain antisyphilitic levels of bismuth concentration in the body X-Ray examination of gluteal regions in patients each receiving adequate antisyphilitic therapy in the form of injection of sobisminol failed to reveal shadows.

Hanzlik has directed attention to the difference in behavior of bismuth acting as anion and as cation. The familiar preparations contain bismuth as cation but he believes there is reason to expect that certain combinations, the bismuthites in which the metal appears as anion, have superior penetrative properties for certain tissues, including especially the nervous system. The claim of bismuth penetration of the nervous system after injection of anionic bismuth is not accepted by all. Klauder (1934) for example failed to find cerebral penetration after injection of sodium iodobismuthite (the bismuth compound in iodobismitol with saligenin N.N.R.) While others have confirmed the presence of bismuth in the cerebrospinal fluid (Strandberg and Sjögren, 1933, Schujman and Macchi Campos, 1935 and Tsing, 1933) While Hanzlik' (1936) impersonal and disinterested reexamination of the question resulted in confirmation of previous positive results, the question is still open. An interesting sidelight of the penetration of bismuth into the central nervous system with possible clinical applications is the finding of Newman and Richardson (1937) that alcoholic ingestion by their experimental animals definitely increased the penetration of bismuth, given as iodobismitol, into the central nervous system.

Circulation, Concentration, Tissue and Blood Distribution of Bismuth.—In general the amount of bismuth in the viscera is determined chiefly by the total dosage of the metal administered. The concentration of bismuth in the blood, ranges in the experimental animal from 1/10,000 to 5/10,000 mg. of metal per gram of blood. If the rate of injection is managed, the highest bismuth level appears at the end of the fourth hour is maintained for twenty-four hours and then slowly declines, the metal being present in minute amounts over a period ranging from weeks to months. Hanzlik (1935) found that the median concentration of bismuth in the blood of patients is of the order of 1:3,000,000 more or less H and his coworkers stat that with the average adult receiving iodobismuthate there is 0 1 mg. of it unchanged in 100 cc of blood Henderson (Cole 1936) places the concentration of bismuth in the blood at 0.05 to 0 1 mg. bismuth per 100 cc. of blood. Hanzlik believes that most of the bismuth in the blood is in the plasma. Bauer and Strauss (see von Oettingen review) believe the bismuth to be bound to the euglobulin fraction of the serum protein but Lomholt found it uniformly distributed through all fractions of the serum, the serum itself containing 78 per cent, and the cellular elements the remainder The striking difference of bismuth from other metals is indicated in its absence from the erythrocytes (compare lead)

The concentration of bismuth in the organs of the body after intramuscular injection is high

which is, of course less with bismuth A number of observations on the effect of bismuth upon the blood picture have been recorded and are somewhat conflicting, probably depending on dosage and salt employed In contrast to the marked anemia producing qualities of mercury bismuth may produce a temporary slight reduction in erythrocytes followed by a definite rise. According to Marcozzi and Neuber the absolute and relative characteristics of the leukocyte count are also slightly affected. (cf Fishback and Fishback, 1937 polymorphonuclear increase in rabbits) Ramsey Brown Saleeby and Schamberg have shown that the effect on renal and nitrogen eliminative capacity and metabolism is dependent on injury to the kidney Administration of bismuth in amounts such as are used in the treatment of patients with syphilis causes abnormal changes at the site of provisional ossification of growing long bones A succession of courses of bismuth treatment gives rise to a series of cross striations radiologically more dense than the normal bone between them As the bone grows the dense bands become further removed from the epiphyseal line and they become less distinct and eventually vanish Although these changes are evident only during the process of bone growth and represent abnormalities of bone growth prolonged bismuth administration does not interfere with the rate of linear growth (Ruskin, Stadler and Jeans, 1942)

Pharmacology of Bismuth.—Considerable advancement of our knowledge of the pharmacology of bismuth compounds is due to the prodigious effort of several American groups of pharmacologists and chemotherapeutists including Sollmann and Cole, Hanzlik, Kolmer and their coworkers

Absorption.—Many of the general principles governing the absorption of heavy metals have been worked out or elaborated in the intensive chemical study of bismuth. All bismuth preparations injected into the musculature produce necrobiotic and necrotic processes as has been stated The injury is least marked with water and tissue-soluble preparations, is more distinct with water-soluble and tissue-insoluble preparations, and is very marked with aqueous and oily suspensions of insoluble bismuth salts. Suspensions of *colloidal metallic bismuth seem to produce somewhat less injury than the* suspensions of the insoluble salt but the regenerative process seems to extend over a very long period. Tissue- and water-soluble preparations are the most rapidly absorbed followed in order by the water-soluble and tissue-insoluble preparations, the aqueous and oily suspensions of insoluble salts and finally the suspensions of colloidal metallic bismuth which show the slowest absorp*tion from the site of the injection. Insoluble bismuth soap formation has* been confirmed by Aubrey for man, in the case of the hydroxide.

Systemic absorption of bismuth compounds in animals is demonstrated by determining the toxic effects and fatalities with large doses, by the rat of disappearance of bismuth compounds from sites of injections and by their appearance in the urine after administration by various routes—intramuscular or oral.

The study of bismuth absorption by the use of the -ray originally applied to mercury hile recognized as practically valuable method in man is shown t contain serious factors of error due in part t the deposition of calcium t the injection site Some of the differences in published results are probably due to difference in the rate of bsorption hich has been show by Cole by Grabert, nd by Montague to be due to the difference in the rat of absorption from fatty tissue nd active and inactive muscular sites. Sollmann and Henderson (1936) have shown in dogs, for example that thiobismol is absorbed practically completely in t hours. With sod um tartrat and presumably other compounds studied, the amount absorbed increased materially beyond three hours. Between eighteen and fifty-one hours, there is little further absorp-

excreted in considerable amounts by the kidney after twenty to thirty days or longer. Massage of the injection sit can produce the ppearance of the metal in the blood within two hours in dogs, the ppearance being delayed t enty-four hours without massage. The most rapid elimination occurs with the water-soluble salts, such as sodium bismuth tartrat (Hanzlik) and sobisminol. (Hanzlik et al. 1936, Sollmann et al. 1938.)

It ppears that several factors are involved in the excretion of bismuth after intramuscular injection (Von Oettingen). The most important are the solubility and the difference bet een aqueous and oily suspensions. The ater-soluble preparations are promptly excreted and the excretion, after having reached the maximum, decreases rather rapidly. When suspended in oil the soluble preparations because of slower bsorption are excreted more slowly. Insoluble preparations suspended in water are excreted more rapidly than those suspended in oil and it seems that the type of excretion of the oil suspension depend also on the chemical composition of the bismuth compound (cf. Cole et al. 1938). The slowest excretion occurs with colloidal metallic bismuth preparations. The age of the patient and the condition of the circulatory and excretory apparatus is of importance for Hanzlik and associates have shown that the excretion of bismuth is perceptibly smaller in edematous patients than in normal persons. The excretion of bismuth is delayed by doses sufficiently large to injure the kidney. Hanzlik, M rtens nd coworkers found that increasing the dosage of bismuth products tends to reduce the total urinary excretion independent of the time factor and regardless of the bismuth product and the vehicle used. They strongly emphasize the objectionable and dangerous character of insoluble products of bismuth and insoluble vehicles from the standpoint of dangerous cumulative effects. They insist that in many cases the vehicle is quite as important as the drug. Corson, Decker and Williams (1940) were able to induce urinary excretion of bismuth from patients with bismuth depots by oral administration of ammonium chloride.

In the case of bismuth administered orally there is definite urinary excretion but the major portion of the metal excreted is by the fecal route. Considerable amounts of the bismuth of sobisminol are presumably retained in the body (probably in the intestinal wall) supposedly t be excreted gradually over long periods in minute quantities. Bismuth ppears in the urine beginning the day after administration nd reaches peak on about the fourth day after single doses (sobisminol) and on the tenth and t enty-eighth days after from 3 to 12 doses respectively. Sollmann, Cole and Henderson (1938) showed that the oral administration of sobisminol in doses of 3 capsules (140 mg. bismuth) and of 9 capsules (420 mg. bismuth) daily for three weeks gave curves of urinary excretion resembling closely the course and degree of those given by the intramuscular use of the water-soluble and oil-soluble preparations. The dose with the oral preparation, however had to be higher than ith the intramuscular preparations. Hanzlik and his coorkers (1937), found the urinary excretion greater after intramuscular injection of sobisminol than after oral administration. (Confirmed by Brown and Kolmer (1942) for sobisminol and potassium bismuth tartrate.) Urinary excretion was demonstrable one half hour after oral administration. Such urinary excretion as found to vary directly with the dose, to manifest cumulative tendency and to outlast the period of administration. Urinary excretion wa retarded or reduced by the presence of food and varied considerably with the individual.

The Toxicology of Bismuth.—The toxicity of bismuth in syphilological practice is remarkably low. In fact, it is so low as to lead the incautious easily into such definite abuses of the drug, as its intravenous administration. The symptoms of severe bismuth intoxication, made familiar by clinical and experimental experience include loss of appetite, vomiting and diarrhea, followed by stomatitis with ulceration of the tongue, severe necroses of the gums tongue and buccal mucosa and black deposits of bismuth sulphide in the mucous membranes. Weakness, slowness and incoordination of movement develop terminating with tetanic convulsions, paralysis and death.

A striking feature of the postmortem picture in animals is the black discoloration of the cecum limited very sharply by the ileocecal valve and extending throughout the thickness of the bowel wall. Lucke and Klauder found that after the tartro-bismuthate pronounced changes occurred in the epithelium of the convoluted tubules of the kidney with degeneration and deposition of calcium salts, as in all heavy-metal poisoning. Kolmer, Brown and Rule (1939) found that this injury is the same for all bismuth compounds studied and believed the responsible substance was elemental bismuth, view supported by Longly, T tum and Clausen (1940–1941) ho believed that bismuth compounds ultimately act in common manner probably due t

common end product and the variations in toxicity and therapeutic activity of different preparations may be accounted for largely by the differences in the rat of absorption from th intramuscular depots. I general the toxicity of bismuth compounds is conditioned by the route of administration, chemical constitution, solubility (the more soluble, the more toxic) and vehicle The bismuth content evidently does not have so definite relationship t toxicity as is generally believed (Kolmer Brown and Rule, 1930). The glomeruli are relatively unaffected The lesions in the liver are less conspicuous, but fatty infiltration and focal necroses may occur Beerman has collected the available literature on fatal bismuth intoxications in man. They are fortunately very rare. Hahn (1941) found only one f tality attributable t bismuth among the 19,580 patients treated with bismuth in Johns Hopkins Hospital between January 1924 and June 1940 (one fatality t pproximately 175,000 injections of bismuth subsalicylate) Acutely fatal intoxications have most frequently followed intravenous injection and take the form of species of colloidoclastic shock. Sudden collapse syncope with respiratory difficulty cyanosis, disappearance of the pulse and convulsive movements usually terminate within few minutes in death. In the more protracted intoxications in man the structures evidently principally involved are the gastrointestinal tract, the liver and the kidney The remarkable margi which exists between the curative dose and the maximum tolerated dose in animals (the rabbit, used in these experiments, however is very tolerant of bismuth) is well indicated by the statement (Kolmer Brown and Rule, 1930) that bismuth subsalicylate is tolerated up to 800–1000 mg per kilo (hite rats) while 6 mg per kilo is the minimal curative dose in rabbits.

Clinical Reactions to Bismuth.—In order to save space a summary and classification of all known forms of bismuth intoxication are given in Fig. 75 which summarizes especially the very large French experience, probably the largest of any single national group as presented in the Reunion of French speaking Dermatologists at Strasbourg in 1930 Among the more interesting and perplexing reactions to the practitioner should be included especially "bismuth grippe, which is at its onset nearly always mistaken for an intercurrent infection but which repeats itself with each injection. Klauder has called attention to the importance of fetor as a sign of approaching chronic bismuth intoxication, a point which we have repeatedly verified It may precede the appearance even of the blue line but as a rule occurs later The blue line is frequently not in reality a line but an isolated segment of discoloration at the contact of the base of one or two teeth with the gum, appearing *most often at the site of a heavy filling or where caries and pyorrhea are in* progress. It is not a contraindication to the continuance of treatment in the majority of cases and, while rather persistent, is to some extent controllable by an adequate mouth prophylaxis as later described. Bismuth pigmentation of the mucosae and gums clears slowly when the drug is stopped Severe bismuth stomatitis appears to differ from severe mercurial stomatitis in a lesser tendency to edema and salivation and a more marked tendency to abrupt necrosis which has been so severe as to suggest an agranulocytic factor in one reported case with hemorrhages into the skin.

The mechanism of bismuth stomatitis nd bism th pigmentation of the mucosae as studied by Ascolay is locally t least not unlike that of mercury as studied by Almqvist, Beeson and others in that relat vely insoluble bismuth sulphide is deposited in the capillary walls at sites where hydrogen sulphide is being produced by putrefactive decomposition of proteins under saprophytic bacterial action in the mouth. Presumably this explains too the deep pigmentation in the alls of the cecum especially The bismuth sulphide acts as local irritant, causing necrosis with hemorrhage and breakdown of the involved tissues in severe cases. The rational remedy as in the case of mercurial stomatitis, is direct attack on the foci of saprophytic infection in the mouth by vigorous dental preparation and prophylaxis Even though it leads all other forms of reaction as cause for discontinuance of treatment (see Fig 76) stomatitis is relatively much less import nt in bismuth tha in mercurial therapy even prophylactic precautions being capable of considerable relaxation (See Chapter IX.)

Fig. 75

TOXICOLOGY OF BISMUTH

I. **Local Reactions at Injection Site**

Pain and induration: Dependent largely on salt, state of division of drug, vehicle and technic. There is also a rare local anaphylactoid reaction with pain, enormous swelling and fever (Gougerot, Stokes)

Arterial embolism: Occurs once in every 8,000 to 15,000 intramuscular injections (Sulzberger and Baer). Four types as follows (Petges and Joulia, Barthélemy *et al.*, Gammel) due to emboli of bismuth or oil in the superficial capillaries

(*a*) Local exanthem—a roseolar eruption around the injection site

(*b*) Phlyctenular and ecchymotic plaques (venous embolism)

(*c*) Livedo (bluish network) and superficial necroses of the skin (at site of exanthem)

(*d*) Deep gangrene due to arterial embolism (fat, or in whole at injection site, or thrown to a distance, glans penis (Kimberly)), bladder wall (Cole). Preceded by sudden, violent pain, pallor of the affected part. May be followed by foot drop.

Abscess: Early or delayed (Vigne Fernet) may be fatal (Foged)

II. **Systemic Reactions.**

Nitritoid or vasomotor crisis (following both intravenous and intramuscular use).

"Colloidoclastic shock" Collapse and death immediate or preceded by jaundice, stomatitis, and delirium usually following intravenous use

Embolic symptoms (regional). Pulmonary cerebral, due to the injection mass, not the drug.

"The bismuth asthenias" (*a*) Simple with cephalgia, rheumatoid pains, backache weight loss; (*b*) "bismuth grippe, with aches and pains and fever suggesting acute infection followed by weight loss; ( ) grippe with psychic symptoms (impotence (Cayrel), crises of respiratory anxiety)

Stomatitis Fetor often first symptom (Klauder). Blue line due to deposition of bismuth sulphide (insoluble) by interaction with H_2S from mouth organisms. Gingivitis due to bismuth sulphide irritation. Ulceration, mucous casts. Blue or blue-black spots (sulphide deposits) (Ascoley McCarthy and Dexter). Necrosis of the jaw and tongue. **Vincent's angina** (*Arwyl-Davies*) (*agranulocytosis?*).

Cervicovaginal melanosis of *stomatitis* (Wiener; (vaginal) Clement Simon), may be spotted, erosive, ulcerated, scarred. Mild processes asymptomatic and unnoticed, severe type rare.

Gastro-intestinal tract (Rare) (*a*) Abdominal cramps, diarrhea (*b*) ulcerative enteritis and colitis (Millan) Melanosis of colon.

Nervous system Vagosympathetic disturbances (vertigo, suffocation, sweating, palpitation, respiratory crises) Polyneuritis (Critchley) Herpes zoster (Becker) Insomnia, nervousness.

Skin: (*a*) Urticaria; (*b*) general edema (Vigne) (*c*) purpura; (*d*) erythemas, morbilliform and scarlatiniform Nicolas *et al.*; ( ) erythrodermias and exfoliative dermatitis due to arsenicals and bismuth (Jordan and Osborne) (*f*) seborrheic eruptions; (*g*) lichenoid eruptions; (*h*) papular exanthem (Lutz-Pautrier resembling syphilid.) Pityriasis-rosea-like eruption (Skolnick and Aleshire) ( ) Pemphigoid eruption, Irgang, Sala and Alexander; Shaffer and Collins (*j*) Miliaria-like eruption. (*k*) Bismuthia (blue-black bands, covered parts grey reactivation of latent argyria (?), Gougerot and Blum Loeth, Sutton, McMullen and Muehlberger) Bismuth may reduce argyria from silver arsphenamine (Spiegel)

Liver Jaundice Nomland *et al* Kulchar and Reynolds, Gott and Doyle Lane (focal necroses) Acute necrosis of liver (Wolman) Rare

Kidney (Rare) (*a*) Polyuria (Blum) (*b*) albuminuria (and stomatitis, Peters; in tropics, Wells and Sewell); (*c*) hemorrhagic nephritis (Gallot, Aubertin and Destouches, Shaffer and Collins) (*d*) oliguria and anuria (Gatt and Moutier Eltsen).

Blood Evidence of slight erythropoietic disturbance still uncertainly defined. Rare agranulocytosis.

Arthralgia (Gemmer)

Therapeutic shock effects Not properly classifiable as bismuth reactions.

The cutaneous manifestations are now well recognized in man urticaria and general edema with the development of brawny plaques and the various forms of toxic erythema being the most frequent, but all forms of cutaneous reaction being in reality quite rare The remarkably low toxicity of therapeutic doses for the kidney is evidenced by the relatively few reports of significant renal damage Hudelo and Rabut having observed albuminuria only four times in 10 000 injections.

The order of importance of clinically observed reactions can be gauged by the frequency with which they force the stoppage of treatment as presented in Fig. 76 from Vigne s summary of 76 478 injections at the Strasbourg Reunion. Carrera in 42,000 injections saw weight loss 6 times, herpes zoster 5 nitritoid reaction 4 stomatitis (severe) 3 skin eruptions 3 absolute intolerance 2 cases.

Vehicles and Routes of Administration of Bismuth.—Bismuth remains, in spite of pharmaceutical propaganda, a one-route drug and its administration by intramuscular injection is the only method countenanced by scientifically grounded present-day practice. Oelze, Lomholt, Klauder and Kolmer (1935) have demonstrated the relative uselessness of bismuth inunctions the drug

Fig 76

PERCENTAGE DISTRIBUTION OF BISMUTH REACTIONS IN SYPHILIS TREATMENT MARKED ENOUGH TO REQUIRE DISCONTINUANCE OF THE DRUG (VIGNE)

	Per cent.
Stomatitis	72
Asthenia and grippe	10
Local pain (severe)	9
General reactions	6
Cutaneous eruptions	5
Abscess	3 3

Vigne estimates that of all reactions, 8 to 10 per cent will require stoppage of the drug.

by mouth is comparatively effective, however when administered in the form of sobisminol mass (sodium bismuthate soluble Hanzlik) Attempts have been made to give bismuth salts intraspinally (Gallardo, Lafora, Agramunt) but the method is dangerous and has no evident advantages. The high toxicity of intravenous administration can be realized by Kolle s example toxic dose 34 mg. of a 50 per cent aqueous preparation minimum curative dose, 20 mg and again toxic dose, 100 mg tolerated dose 90 mg minimum curative dose, closely approximating 100 mg These narrow margins of safety should be compared with a margin of three to ten times the effective therapeutic dose as compared with the toxic dose on intramuscular administration (Raziss and Severac)

The fatal dose in rabbits and dogs by intramuscular injection is five to ten times higher even when the soluble bismuth compounds are given in dilute solutions by slow intravenous injection "drip method" (Sollmann and Seifter 1942)

Bismuth Preparations in Common Use in the United States.—The number of bismuth preparations available to the physician is legion In order to guide the physician to the better established and widely used preparations, we are

submitting in Fig 77 the preparations described in New and Nonofficial Remedies (1942) of the American Medical Association. By judicious employment of these compounds one may accomplish any desired bismuth therapeutic effect. According to Cole Sollmann and Henderson (1930) one may use the following scheme for bismuth therapy and obtain a more or less continuous urinary excretion of 2 to 4 mgm. of the metal daily which would indicate a satisfactory continuous therapeutic level in the blood stream

For rapid bismuth effect

Sodium bismuth tartrate in water	Injections intramuscularly three times a week
Sobisminol, Iodobismitol	Injections twice weekly

If the patient can be persuaded to return twice a week for injections probably the most efficient preparations in terms of high bismuth excretion are sobisminol and iodobismitol

For a somewhat slower but efficient bismuth effect

Biliposol, Bismocymol	Injections every five days to once a week

For an effect slow in building up but eventually sustained

Injections of oil suspensions of

Sodium potassium bismuth tartrate, Bismuth subsalicylate	Once weekly

For patients with acute syphilis or those sensitive to arsenical, when a rapid but prolonged effect of bismuth is called for Sollmann Cole and Henderson (1938) suggest a graded sequence of soluble bismuth preparations with continued weekly injections of an oil suspended bismuth preparation.

General Dosage Rule for Bismuth Preparations.—While the dosage of the listed preparations is given in the table, it is worth while to attempt a formulation of a general dosage rule for bismuth preparations. This has been undertaken by Lomholt on the basis of the oxychloride, which he has extensively investigated. Lomholt's rule, as it might be named calls for a dosage of 0.5 mg of bismuth metal per kilo of body weight per day In utilizing such a rule it is apparent that the user must know the metallic content of the bismuth preparation he employs and this should be placed by the manufacturer on the label of each bottle or ampule. It must further be recalled that the oxychloride which Lomholt employed carries 80 per cent metallic bismuth and is regarded as one of the best absorbed and best eliminated of available bismuth preparations of the water-suspended group When an oil-suspended preparation is administered the slower absorption and the greater tendency to accumulation must be allowed for The estimate of 0.5 mg per kilo per day is, however conservative for rapidly absorbed and eliminated preparations and where short courses or long rest intervals are allowed may be increased to 0 7 mg with the realization, however that there will be definite accumulation of the drug with insoluble or oil-suspended salts during the period of treatment. The desirable therapeutic level of bismuth in the blood stream as indicated by a satisfactory daily urinary bismuth excretion (2 to 4 mgm.) may also be attained by using the bismuth preparations as classified by Cole, Sollmann and Henderson (1939) (abov) Thus, for a man weighing 65 kilos

Fig 77

BISMUTH PREPARATIONS FOR TREATMENT OF SYPHILIS LISTED IN NEW AND NONOFFICIAL REMEDIES, 1942

Trade name	Chemical constitution	Preparation.	Approx. per cent Bi.	Single therapeutic dosage in man.		Frequency of injection.	Manufacturer or distributor
				Compound.	Metallic Bi.		
		For Intramuscular Use *Water Soluble*					
Bismosol	Potassium sodium bismuthotartrate.	Solution glucose.	35	1 cc. (0 1 Gm.)	0 035 Gm.	3 weekly	Merck.
Bismuth sodium tartrat	Basic sodium bismuth tartrate.	Solution sucrose.	72 7–73 9	2 cc. (0 03 Gm.)	0 022 Gm.	3 weekly	Searle.
Potassium bismuth tartrat	Basic potassium bismutho-tartrat	Solution sucrose.	64	2 cc. (0 06 Gm.)	0 032 Gm.	3 weekly	Abbott.
Thiobismol	Sodium bismuth thioglycollat	Dispensed as powder soluble in water	38	0 2 Gm.	0 076 Gm.	3 weekly	Parke, Davis.
Iodobismitol with benzocaine	Sodium iodobismuthit (Sodium bismuth iodide) and benzocaine	Solution propylene glycol.	21	2 cc. (0 115–0 133 Gm.)	0 024–0 027 Gm	2 weekly	Cutter Squibb.
Sobisminol solution.	Undetermined as yet.	Propylene glycol and water	10 25–20 25	2 cc. (0 2 Gm.)	0 030–0 041 Gm.	2 weekly	Cutter Lilly Squibb.
		Oil Soluble					
Bismocymol	Basic bismuth camphocarboxylate.	Solution olive oil.	37–40	1 cc. (0 13 Gm.)	0 05 Gm.	2 weekly	Abbott.

Oil Suspended							
Potassium bismuth tartrat	Basic potassium bismuth tartrat	Suspended in olive and almond oils	64	2 cc. (0.2 Gm.)	0.128 Gm.	weekly	Abbott.
Bismuth subsalicylat	Bismuth subsalicylate.	Suspended in peanut oil.	58	2 cc. (0.2 Gm.)	0.114 Gm.	weekly	Abbott and numerous others.†
Oleo-bi	Bismuth oleat	Suspended in olive oil.	19.8	2 cc. (0.05 Gm.)	0.100 Gm.	eekly	Hoffman-La Roche.
Tartro-quinobine	Quinine bismuth iodide 0.072 Gm. (18–20.1 per cent Bi) and sodium potassium bismuthyl tartrat 0.032 Gm. (40.75–41.25 per cent Bi).	Suspended in olive oil.	27	1–2 cc. (0.1–0.2 Gm.)	0.027–0.054 Gm. approx.)	2 weekly	Alba.
Combination of Bismuth and Arsenic							
Bismarsen	Bismuth arsphenamine sulfonat	Dispensed as powder soluble in water	24 (13 per cent arsenic).	0.2 Gm.	0.05 Gm.	2 eekly	Abbott.
FOR ORAL USE							
Sobisminol mass	Undetermined as yet.	In capsules (0.75 Gm. each)	19.25–20.25	6–9 capsules 4.5–6.75 Gm.	0.900–1.35 Gm.	daily	Cutter Lilly Squibb

Also supplied in 3 per cent solution, each 2 cc. containing 0.06 Gm. of the compound.

† The data given are for typical preparation. Various modifications in vehicle, concentration of compound and local anesthetic are used by different manufacturers.

Bismuth Ethylcamphorate (Upjohn) (bismuth III salt of *d*-camphoric acid mono-ethyl ester) Epsoluble, used 2 cc. (90 mg. bismuth) weekly was accepted for N.N.R. on March 21 1942.

Fig 78.

SOME SUGGESTIONS FOR SELECTION OF APPROPRIATE BISMUTH COMPOUNDS

1 Know th metallic content of any preparation you consider
2. Be content with two or three preparations.
3 Make changes only on authoritative pronouncement i the literature ad by NNR acceptance not detail-man importunity ad leaflet campaigns.
4 Do not expect bismuth to do the work of an arsphenamine especially in early syphilis.
5 As rapid preparatory treatment less likely t produce shock effect than arsphenamine use ater-soluble bismuth salt in aqueous solution.
6 For th routine of bismuth therapy including ordinary preparation for an arsphenamine, use either an oil-suspended w ter-insoluble such as the salicylat or hydroxide which gives good absorption and good elimination with moderate or slight accumulation; or a liposoluble bismuth (camphocarbonat series, et)
7 When patients ar likely to be erratic and irregular; or the rest intervals long or prolonged effect is desired (one course a year) use the older oil suspensions (NaK Bi tartrate) if patient will tolerat some local reaction.
8 When bismuth is used with an arsphenamine at short intervals use preparation with rapid absorption and elimination—e. w ter-soluble Na Bi tartrat thioglycolate, liposoluble Bi t void cumulative effects.
9 When complex tonic and adjuvant effects ar desired, as i debilitated patients, late cases, elderly tabetics, cardiovascular wrecks, et se compound ith quinine, iodide arsphenamine such as the iodobismuthat ith or ithout another salt; or bismuth arsphenamine sulphonate
10 Regulat th dosage and interval by the bismuth ontent and the effect desired, not by single rule of thumb.
11 If injections are to be infrequent (eekly) use the high-metal content, oil suspensions, and give shorter courses (8 t 12 injections, average 10)
12. If intervals are to be short (t t five day) use B as under (8)
13. T reduce local reaction use lipoid suspensions (salicylat double suspensions such as tartroquinobine) liposolubles.
14 W t h the future in the literature of ( ) liposolubles (b) preparations ith special penetrations such as Bi as amon (iodobismuthit) and ( ) oral preparations (sobisminol mass)

the dose of 227 mg per week w uld require that an oil-suspended preparation uch a bi muth subsalicylate containing 65 mg of metallic bismuth per cc

Fig. 79

THE IDEAL BISMUTH COMPOUND FOR INJECTION

1 Constant metallic content and stability of salt.
2. Exact dosage (difficult in suspensions)
3. Post-injection depot absorption in three to seven da s, and i nown longer interval if accumulation is desired.
4 Constant excretion level permitting blood stream circulation
5 No local pain.
6. No abscesses.
7 Tissue-soluble (no granular depots, insoluble soaps, alcification)
8. Self-sterilizing.
9 Freedom from complications such as extens mouth deposits or ttack on special structures such vascular system and bone marrow
10. Good clinical result

(In part fter Cole et al., Ven. Dis. Inf 12, 143 April 20, 1931)

with 130 mg metal per optimum single dose be given e ery four to five days. If gi en on a weekly ba is the dose would ha e to be nearly 4 cc. of the sus-

pension. On the other hand a preparation such as quinine iodobismuthate with only 30 mg. bismuth per cc would have to be given in 2 cc. doses three times or more per week or in large single doses of 6 cc. weekly with much discomfort, to approximate the 227 mg optimum of Lomholt's rule. The less frequent injections usually used in clinical practice with the oil-suspended preparations allow for their slower and more erratic absorption.

An interesting commentary on the influence of total dosage of bismuth is presented in Hugo Müller's discussion of relapse under bismuth therapy (Jadassohn Handbuch) in which he discusses the dosage practice of Germany and France during the earlier years of the bismuth era. The emphasis of the French on bismuth led to a larger dosage per course and a larger total dosage, the amount administered being 1.6 to 3 Gm. bismuth metal in each series of injections. Earlier German practice, on the other hand, contained numerous reports of relapses, apparently based on a dosage approximating 0.75 Gm. Bi metal per course. German practice, according to Müller, early adopted the principle of simultaneous use of the arsphenamines, thus doing away with the tendency to relapse and escaping the disadvantages apparent in French practice for a time of albuminuria and other bismuth complications. Müller furthermore insists that the condition of the German population with respect to nutrition and resistance following the First World War was such that the large doses of bismuth could not be tolerated. In recent years the average dose per course in Germany has risen to 1.5 Gm. bismuth metal in combined therapy and 2 Gm. when used alone. It has also been contended that the quinine-iodine-bismuth combinations are as effective in smaller doses as the metal alone or in simpler combinations in larger doses. It will be apparent that giving the Lomholt optimum, 2 to 2.3 Gm. bismuth metal per ten-injection course is the more or less accepted practice of the present day

Rest Intervals with Bismuth.—The rest interval between bismuth courses must allow both for the absorption of the deposit depots and the return of the tissues to a condition favorable to further therapy When the larger doses of bismuth are being used a shorter interval than six weeks scarcely allows time for these changes to take place between courses and eight weeks is frequently desirable. If on palpation nodular deposits can be recognized before the beginning of the second course, the same caution should be observed which was familiar under the insoluble salt regimen in mercurial days. A nodular or indurated injection site means retained metal and may at any time, under unexpected trauma or other influences, give rise to toxic absorption It is, therefore, undesirable to use preparations giving rise to sharp local reaction and nodule formation in certain individual cases or to carry any bismuth course to the point of deep protracted and resistant infiltration of the injected tissues. In the case of oral bismuth medication (sobisminol mass) sustained therapeutic effects from the drug are obtained only during the period of administration. If treatment is stopped the antisyphilitic effect appears to stop (Scholtz, McEachern and Wood, 1939)

Clinical Effects of Bismuth in Syphilis.—While the action of a soluble bismuth salt is quite rapid, it does not equal that of the arsphenamines and may even be approached by that of a water-soluble mercurial salt administered daily Lévy's results indicate that there is little difference between the water-soluble and the liposoluble bismuth preparations in their spirillicidal action. Both of them, however are distinctly more effective than the insoluble preparations. Oral bismuth medication with sobisminol mass seems to produce clinical antisyphilitic effects comparable to those produced by bismuth administered intramuscularly but the time of observation is as yet too short for final evaluation. (Meininger and Barnett, 1939 Scholtz, McEachern and Wood, 1939)

Under vigorous treatment with a soluble bismuth salt, small primary lesions have been known to heal in from one to four or five days but the average course more nearly approximates

two or even three weeks, when involution of the induration is taken into account. The rate of disappearance of secondary syphilids varies with the type of lesion but has been well summarized by Fournier and Guénot, who found that mucous patches were healed in four to five days, the organisms disappearing by the first or second injection. Hypertrophic papules heal in several days and are resorbed in ten to twenty-five days. Simple roseola disappears in five to ten days, often with Herxheimer reaction lasting twenty-four hours. Papular eruptions require an average of 5 injections and an upper limit of 10, the time required ranging from fourteen to thirty-five days. Papulopustular eruptions require 10 to 12 injections with approximately the same time. Late syphilids of the skin and mucous membranes have impressed us as disappearing distinctly more slowly under bismuth than the early syphilids and definitely more slowly than under the arsphenamines. On the other hand, Fournier and Guénot reported the disappearance of serpiginous syphilids under potassium bismuth tartrate in ten to nineteen days and Duerty and Müller reported the astonishingly rapid disappearance of the notoriously resistant keratoses of the palms and soles after 2 or 3 bismuth injections. Gummatous lesions of the lip and nasopharynx respond rapidly 8 to 10 injections being an average requirement, but Müller reported a remarkable case with erythema-multiforme-like lesions and extensive destructive lesions of the pharynx which disappeared following 1 injection of Trepol. Relief of pain is said to be as striking as after arsphenamine when the drug is employed alone. Leukoplakia has been reported as responding, but our own experience accords with that of Simon and Müller to the contrary. The superiority of bismuth to mercury can be readily recognized in the now comparatively rare malignant syphilis. Azoulay reports a case of generalized papulopustular and ulcerative syphilid with fever that failed to respond to 30 mercurial injections but was healed in ten days with quinine iodobismuthate. Sobisminol mass orally caused disappearance of spirochetes in a median of four to five days from seropositive primaries and involution of the lesions in a median of fourteen days. Secondary lesions disappeared in about two weeks. Gummas were healed in from about three to five weeks. (Meininger and Barnett, Scholtz, McEachern and Wood, 1930.)

The response of visible syphilids to bismuth is as in the case of arsphenamine and the disappearance of spirochetes, one of the few clearcut ways by which the practitioner devoting himself to this work can measure the effectiveness of his bismuth preparations and his dosage and plan of treatment. It is for this reason that the foregoing details have especially been given. This statement, however, should not be interpreted as encouraging the use of bismuth alone in the treatment of early syphilis as a routine, for the concomitant use of the arsphenamines, as will be seen later, is absolutely essential.

Bismuth in Osseous Syphilis.—The action of bismuth in syphilis of the skeletal system is prompt and satisfactory, certain types of headache and joint pains in early syphilis disappearing in one to two injections. The action in osteitis, osteomyelitis and bone gumma is markedly superior to that of mercurials and iodides. Late syphilids of the septum and palate, often so notoriously resistant to both arsphenamine and mercury, may respond surprisingly to bismuth, as in the case reported by Müller in which healing of an extensive process followed two bismuth injections.

Bismuth in Hepatic Syphilis.—In syphilis of the liver bismuth is well tolerated in the early cases and the drug is particularly serviceable in those cases of complicating catarrhal jaundice following on previous arsphenamine administration in which it fills a wide gap between the poorly tolerated arsphenamine and the relatively ineffective mercury. In late syphilis, however, great caution in dosage must be observed if too rapid an effect is not to be secured, and we personally believe that there mercury and iodide is still the preferable treatment.

Bismuth in Renal Disease.—In renal disease, whether due to syphilis or not, bismuth has a distinctive place in treatment. Müller has observed good effects from bismuth in treatment nephrosis which made the use of either arsphenamine or mercury, previously employed, impossible.

Bismuth in Cardiovascular Disease.—The question of the effectiveness of any single drug in the treatment of syphilitic cardiovascular disease cannot be decided merely by symptomatic response as will be brought out in a subsequent chapter. It may, however, be said in general that bismuth is able to produce marked symptomatic improvement when very cautiously administered in aortitis and aneurysm. Lacapère and Laurent and Perrin have reported the recession of aneurysm under treatment. Wodtke also observed favorable results in connection with arsphenamine therapy. Blackford and Boland have reported good results from bismuth alone in congestive heart failure in syphilitic patients. The influence of bismuth as a diuretic in patients suffering from breach of compensation is considerable and points to the use of a salt such as the water-soluble sodium bismuth tartrate if such effects are desired. Hypertension associated with syphilis tolerates bismuth better than mercury but with uncertain outlook for improvement.

On the other hand, in severe cardiac involvement, especially with decompensation, we believe bismuth has serious dangers and the utmost caution must be used in its administration if it is employed at all. One of us (J. H. S.) has observed three deaths occurring within twenty-four hours after single injections of potassium bismuth tartrate in which there was no reason to expect a fatal outcome from the general aspects of the cases. Müller observed the sudden onset of dyspnea and pain over the heart in a previously compensated case following 0.25 Gm. bismuth, and states that 5 mg. of metallic bismuth should never be exceeded as an initial dose in cases exhibiting cardiac complications. Unfavorable effects on the coronary system are especially to be feared.

Bismuth in Neurosyphilis.—The action of bismuth in neurosyphilis has been extensively studied. While there can be no doubt of the response of individual lesions, including gumma, meningitis, myelitis and isolated nerve lesions, the general effect of the drug is inferior to that of a properly directed arsphenamine therapy so far as spectacular action is concerned. On the other hand, its slightly slower action is a positive advantage in the majority of cases in that it avoids sometimes serious therapeutic shock effect. While neurorecurrences have been known to occur where bismuth therapy was employed to the exclusion of arsphenamine in early syphilis, the slower and more prolonged action of the drug has been apparent in their postponement until some time after the cessation of treatment. The very interesting observations of the Breslau clinic on the incidence of neurorecurrence during the period that the German insurance clinics were forbidden the use of arsphenamine for reasons of economy indicates distinctly that the drug should not be used alone with the expectation that it will prevent relapse in the nervous system in early syphilis. Neurorecurrence after bismuth therapy has even been observed to clear up with the subsequent administration of mercury (Galliot).

In tabes the symptomatic effect of bismuth is notable and often gratifying. Bismuth alone, especially in the iodoquinine combinations and the more soluble salts, often gives surprising responses in lightning pains and may very favorably affect gastric crises. In optic nerve involvement bismuth theoretically escapes the disadvantages of the arsphenamines and yet should be superior to mercury. Improvement in bladder function, which is in some ways a species of test of the effectiveness of a system of treatment in tabes, has been observed under bismuth therapy alone (Scherber). Improvements in gait, in

libido and potentia, disappearance of Romberg sign, optic atrophy brought to a standstill or definite improvement in vision, are all recognized good effects Response to bismuth usually occurs early in the course, if it appears at all

In the therapy of paresis there is no justification for the use of bismuth alone and its combination with fever therapy and tryparsamide is not yet evaluated Vonkennel has shown that the content of bismuth in the cerebrospinal fluid is increased during exacerbations of fever in malaria. The favorable effect of bismuth on cerebrospinal fluid abnormalities is now demonstrated beyond question, the principal effect being upon cell count and globulin content rather than on the Wassermann reaction. Artom (see Handbuch) has stated that the order of recession of the findings is lymphocytes, colloidal reaction globulin reaction and Wassermann, a statement more or less true of all forms of combined treatment.

Bismuth serves at the present time best as a means of securing rather quick symptomatic improvement in nonparetic neurosyphilis without the risks of the arsphenamines and with the avoidance of therapeutic shock effects

Bismuth in Eye and Ear Syphilis.—In the acutely inflammatory processes, such as iritis, iridocyclitis, neuritis and neuroretinitis bismuth's superiority to mercury has already been demonstrated. A number of communications attest its harmlessness in primary optic atrophy (see Müller Handbuch, p 357) Interstitial keratitis responds to intensive bismuth therapy but we believe more slowly with oil-suspended insolubles than to arsphenamine or to the combination of arsphenamine and a soluble mercurial salt. In one patient one of us (J H S.) was able to watch the difference in effect between potassium bismuth tartrate in full doses intramuscularly once a week and the much more rapid progress made under mercury succinimide, a soluble mercurial salt, given four or five times a week. Both drugs were administered simultaneously with arsphenamine. The tendency to relapse and progress under the insoluble bismuth salt was controlled satisfactorily by the soluble mercurial. When bismuth is employed for these purposes it would therefore seem advisable to give preference to a water-soluble, frequently injected salt such as sodium bismuth tartrate

Syphilis of the eighth nerve responds well to bismuth and inasmuch as the injections need be given less frequently than in the case of a soluble mercurial convenience may dictate its use. It avoids the risk of localized therapeutic shock effect in the eighth nerve involvement of early syphilis. Syphilitic labyrinthitis responds favorably according to Pasini

Bismuth in Pregnancy—*Bismuth can be expected to make a very important contribution to the treatment of the syphilitic pregnant woman,* in view of its high renal tolerance and its comparative freedom from shock effects. Supposed abortifacient effects from bismuth led Pouget to disapprove of its use but no general objection on this score has appeared. Juliusberg (Handbuch) calls attention to the necessity for considering this possibility in the use of the quinine iodobismuthate the effect, however being due to the quinine and not to the bismuth. It is not, however advisable in the treatment of early syphilis to employ it to the exclusion of arsphenamine. Castallo and Rakoff (1938) found that quinine iodobismuthate afforded little protection to the fetus and was markedly inferior to arsenical therapy In late syphilis, however it has the great advantage of being much less likely to disturb the woman's immunity mechanism and can be used with reasonable caution throughout the pregnancy Klaften has demonstrated the feasibility

of combined bismuth-arsphenamine therapy using as high as 3 to 4 Gm of bismuth metal. This is now routine practice in the treatment of syphilis complicating pregnancy

Bismuth in Prenatal (Congenital) Syphilis.—The use of bismuth to the exclusion of other drugs in the treatment of prenatal syphilis has strong advocates both in this country and abroad both on the ground of excellent symptomatic effect and the fact that in the majority of its manifestations prenatal syphilis is a form of late syphilis (see Chapter XXI) in which the immunity mechanism and tissue defence are important and should be disturbed as little as possible in securing symptomatic results Wright has been particularly active in this country in advocacy of exclusive bismuth treatment for prenatal syphilis. Personally we believe that it should be used with arsphenamine as subsequently outlined.

Dosage scales for the use of bismuth in the prenatally syphilitic child began, for example, with 2 mg. per kilo (Hoffmann) 5 mg per kilo (Drouet) 1 to 5 mg. (Vigne and Galliot), using such preparations as the salicylate. Of the iodobismuthates the initial dose may be 2 mg. per kilo. Müller restricts himself to 2 to 3 mg. per kilo. Wright used 5 mg. per kilo of potassium bismuth tartrat with excellent results. Stokes and Ingraham use 2 to 4 mg per kilo body weight of bismuth metal eekly Injury to the kidney need no more be feared in infants and children than in adults.

Effect of Bismuth on the Blood Serological Reactions.—Sazerac and Levaditi demonstrated the possibility of reversal of the blood serological test by bismuth alone in their early studies on the effect of the drug. None the less, the behavior of the serologic reaction under bismuth differs distinctly both in our experience and that of a number of other observers, from the response of these tests under arsphenamine and mercury In seronegative primary syphilis there is a distinctly greater tendency to fluctuation with the appearance of weak positives alternating with negatives so that the drug seems somewhat less effective in holding the initial seronegative state of the patient in seronegative primary syphilis. Similarly the proportion of serological reversals secured in the early weeks of the disease is less under arsphenamine-bismuth than under arsphenamine-mercury therapy On the other hand, as shown by the studies of the American Cooperative Clinical Group the early difference in favor of mercury is ultimately met by the superior results of arsphenamine-bismuth therapy The more rapid action of the mercurial combination was apparent in the first three months. Emory and Morin Ducrey Pasini, Bloch and Radaeli have all noted this delayed action of bismuth and Martin, Nathan and Martin noted a high proportion of fluctuating though ultimately negative tests. A second effect of bismuth therapy on the serological tests is a distinct tendency to provocative action leading to the development of positive serological tests in patients previously negative during a rest period The recrudescence of the positive is followed by a slow but ultimate subsidence to negative under treatment, the patient often tending to remain positive (and correspondingly disappointed) for weeks or months after the completion of the activating bismuth course Provocative effects from bismuth have been repeatedly observed (Biberstein Müller and Kohlenberger) The influence of bismuth, intramuscularly administered, in the reversal of fixed positive serological tests has been favorably reported. The effect is probably as much that of a change in the angle of attack as anything

else. Bismuth therapy given simultaneously with arsenical seems to have a delaying effect on serologic reversal (Beerman 1939)

McCafferty and MacGregor reported 61 7 per cent response in 25 cases that had failed to undergo reduction in the intensity of the serological test in spite of prolonged treatment with arsphenamine and mercury Only 20 per cent, however achieved complete negatives. Simon reports 5 complete reversals in 8 cases.

Bismuth resistant Syphilis.—The existence of absolute resistance to bismuth is now fully established but is a comparative rarity comparable to arsphenamine resistance and certainly much less frequent than resistance to mercury

The presence of active *Spirochaeta pallida* in the primary lesion after 13.5 Gm. bismogenol was observed by Elmassow-Sternberg and Levy Metzger observed similar case in which there was subsequently immediate response to mercury cyanide. The steady progression of secondary syphilitic manifestations under 7 bismuth injections totalling 1 12 Gm. Bi was observed by Lortat-Jacob, and Roberti. Müller observed the excellent effect of repeated change from arsphenamine to bismuth in patient who became resistant first t one and then to the other Lehner observed the absolute resistance of an infiltrated plaque to arsenic, bismuth and mercury Beerman (1936) reviews the literature

Therapeutic Shock (Jarisch-Herxheimer Reaction) under Bismuth.—Therapeutic exacerbation of visible syphilitic manifestations in the primary and secondary stages of the disease can easily be observed with the majority of bismuth preparations and their occurrence in the deeper structures in late syphilis must therefore be inferred. As a rule the reaction is slower in its appearance than after arsphenamine. Böhme, however observed the reaction as early as eight hours after the injection of oil suspensions, including potassium bismuth tartrate. The intensity of the reaction is not necessarily proportional to the bismuth content, being evidently dependent upon the rate of absorption and dissemination of the drug and is said to be frequent with the iodoquinine combinations. The height of the reaction is usually reached by the second or third day after the administration and the course may be materially prolonged.

In the verage experience, the incidence of therapeutic exacerbation is from 15 to 20 per cent (Stirling, Levaditi and others) Edema and swelling of the primary lesion have been observed by Simon, Müller and others. Slight fever may develop in secondary syphilis. Painful lymph node enlargement has been observed by Truffi and Müller Milian regards headache following bismuth injection in early cases as therapeutic shock effect.

There is, therefore, abundant reason for caution in the use of bismuth in conditions involving the cardiovascular and nervous systems and the liver in order to avoid significant therapeutic shock effects. Werther has observed a cerebral therapeutic shock effect with signs pointing to localized edema of a focus in the internal capsule with recovery under silver arsphenamine. The known vasculotoxic effects of bismuth may well be added to therapeutic shock effects in dealing with cardiovascular syphilis, especially with coronary involvement.

Bismuth as Prophylactic.—Kolle experiments on the spirochetostatic effects of bismuth and its inhibition of development of the primary lesion have led to attempts to use the drug as prophylactic. The problem of systemic prophylaxis of syphilis is discussed in subsequent chapter but it may be said that in general it is more likely that the effort t use bismuth in this

way will simply cloak the asymptomatic invasion of the body by the *Spirochaeta pallida* rather than actually prevent infection. Sonnenberg and others (Ramljean and Tran-Tan-Phat, 1937 Lepinay and Levaditi, 1936) attempted the immunization of prostitutes with bismuth by injection and by mouth, with suggestive results. This was not confirmed by Rabut (1936) and Gaté and Cuilleret (1936) Sobisminol mass orally has not as yet been tried in human prophylaxis (Hanzlik, Lehman and Winkle, 1940) On the other hand, syphilis has been observed to develop in patients under active bismuth treatment for other purposes (Pinard) and Kolle experiments with bismuth "plugs" are being subjected to more conservative interpretation.

Contraindications to the Use of Bismuth.—Idiosyncratic or allergic reaction to bismuth is known (see Fig 75) One of us (J H S.) has observed one striking example of local edema of the buttock following the first injection and repeated after the second injection, completely crippling the patient for the time being and making the continuance of the treatment impossible. Exfoliative dermatitis following bismuth injection has been reported by O'Leary and the value of Besredka desensitization is suggested by Stirling. The tendency to permit neurorecurrence in early syphilis contraindicates sole dependence on the drug in this phase of the disease A decompensated heart condition especially with liver stasis, is recognized as a definite contraindication and the utmost caution in dosage must be used. Bismuth must be used with caution in nonsyphilitic hepatic disease In renal disease the presence of albuminuria as such is not a necessary contraindication to the use of bismuth, and Müller states that he has seen the drug even better tolerated than neoarsphenamine in small doses. Smechula has warned against the risk of inducing coma in diabetics through incautious bismuth therapy The kidney even if impaired, seems however to gain in tolerance of treatment for syphilis as McFarland showed for a large arsphenamine-mercury material at the Mayo Clinic and as subsequent studies of complications by the Cooperative Group have tended to suggest. The final strong contraindication to intensive bismuth therapy is the presence of a hemorrhagic diathesis of any type, including paroxysmal hemoglobinuria. The tendency to agranulocytosis should also be borne in mind. In tuberculosis, bismuth is apparently better tolerated than mercury but must be used with caution.

Comparisons of Bismuth and Mercury—A comparison of heavy metals is inevitably more difficult than a comparison of an arsphenamine with a heavy metal, owing to the slowness of action of the latter and the fact that the results must be gauged by such intangibilities as the effect on resistance and defence on the incidence of complications which may require years for their appearance and on the ultimate outcome of the disease It is, therefore, small wonder that comparisons of bismuth and mercury are still largely speculative and impressionistic. The gradual crystallization of opinion in the past ten years has led to two numerical formulations, both French, which fairly summarize present-day opinion. Milian rates arsphenamine as 10 bismuth as 7 and mercury as 4 in a numerical scale More recently Gougerot has revised these figures for his own experience to read arsphenamine 10 bismuth, 8 mercury 6 The discussion of bismuth by Müller in the Jadassohn Handbuch accepts only calomel and the gray oil as even the approximate equivalents in effectiveness of easily available bismuth preparations, at the present time. Conservative stands, acknowledging the usefulness of bismuth, but deprecating the complete replacement of mercury have been taken by De Stefani, Anwyl Davies, Wright (1936) Cannon and Robertson (1936) and ourselves. Lomholt, one of the foremost European students of bismuth and

mercury from the biochemical standpoint, definitely rates bismuth as superior to mercury from every standpoint.

The following facts accumulated by the Cooperative Clinical Group tend definitely to support the superiority of bismuth. The first concerns the incidence of cutaneous and mucosal relapse under arsphenamine-mercury and arsphenamine-bismuth. Of 1117 cases receiving arsphenamine and mercury exclusively 107 or 9 6 per cent, showed mucocutaneous relapse Of 608 cases receiving arsphenamine and bismuth exclusively 22, or 3 6 per cent, showed mucocutaneous relapse The second group of studies with reference to the effect of arsphenamine-mercury and arsphenamine-bismuth on the serological gradient in treated early syphilis has been alluded to. It appears that one year or more (delayed reversal) is required to reverse to negative the blood Wassermann reaction in 8.3 per cent of cases continuously treated with arsphenamine-mercury as against 2.5 per cent with arsphenamine-bismuth A larger proportion of patients treated with mercury therefore, show delayed serological reversal. Under intermittent treatment, arsphenamine-mercury fails to reverse the Wassermann reaction in one year or over in 22.4 per cent while arsphenamine-bismuth fails in only 13.8 per cent. Even with irregular treatment, arsphenamine-mercury fails to secure reversal in one year or over in 50 9 per cent as against 40 8 per cent with arsphenamine-bismuth. The tendency to a more rapid reversal of the Wassermann under arsphenamine-mercury in the first three months and the tendency for this difference to equalize itself and result in an ultimate superiority for arsphenamine-bismuth has already been mentioned (p 211) An interesting controversial sidelight, however is afforded by the fact that in this same series of statistical studies when treatment results were classified by years in the decade 1919 to 1928 no conspicuous jogs," representing advances in clinical or serological results, coincide with the years during which mercury has been in part superseded and bismuth has assumed prominence in the therapeutic methods of the five cooperating clinics One is thus left with the conclusion probably the nearest approach to truth obtainable under the circumstances, that therapeutic results in early syphilis are a matter of balance among the agents employed. Bismuth may support a weaker arsenical, while an effective arsenical may support the inadequacies of mercury In most cases, combined treatment secures a good result before the virtues of any combination are taxed to the utmost.

What Bismuth Does Best.—The influence of bismuth is not as yet fully determined with reference to the following points (1) its effect on tissue resistance and defence (2) any tendency to activate quiescent infections, manifested only by positive serological reaction with resultant progression and complication (3) induction of therapeutic shock in vital structures (4) effect on the prevention of various forms of relapse (5) spirochetostatic power meaning thereby its ability indefinitely to hold ground gained or with appropriate repetition of treatment, to reduce the infection to lifelong latency (6) retention of the drug in the body—how much?—how long? The last item is in process of evaluation through the admirable advances made in the biochemical study of the drug in recent years

Bismuth fits in with the arsphenamines so to speak, early and late in the management of syphilis for its use encourages resistance building at a time when the shortcomings of the arsphenamines in this particular are most serious. Its low toxicity does away with the objections operative in the use of mercury and the arsphenamines and its spirillicidal effect maintains a con

stant check upon the remultiplication of organisms during periods when arsphenamine treatment must be suspended There is, at least thus far no clinical evidence that it gives rise to treatment allergy as do the arsphenamines. Thus it should at least theoretically be possible to keep the early case of syphilis, by the use of bismuth as distinguished from mercury in a noninfectious condition throughout the entire progress of the cure the drug, moreover can be administered for longer periods in moderate dosage without fear of intoxicating effect than can mercury

Bismuth as Preparatory Treatment.—Another accomplishment of bismuth is as a preliminary to the use of the arsphenamines, where there is some fear of therapeutic shock following the initial administration of the drug. So satisfactory is the slower and yet effective action of bismuth in properly graded dosage in this particular and so free from undesirable complications, that it may almost be offered as a general rule of procedure that wherever involvement of the nervous system for example in early syphilis is suspected and in

Fig. 60.

WHAT BISMUTH DOES BEST

1 Fits in with the arsphenamines early and late. May be given with arsphenamine and with proper choice of salt, vehicle and dosage continuously over long period (see chapter on the Treatment of Early Syphilis)
2. Is an adequate, nonreaction-inducing therapy for symptomatic latency apparently not materially disturbing the body resistance and defence mechanism.
3. Effective in late syphilis with minor manifestations, voiding the risks of the arsphenamines.
4. Invaluable in arsphenamine- and mercury-resistant cases, including serological fastness.
5. Invaluable in arsphenamine or mercurial intolerance, especially rsphenamine intolerance or idiosyncrasy in early syphilis.
6. Useful in conditions contraindicating arsenic, as exfoliative dermatitis, liver injuries.
7 Useful in nephroses and impaired renal function.
8. Effective in tolerated dosage in old age.
9 Effective as more rapid preparatory treatment for arsphenamine combining the low toxicity and freedom from shock effects of mercurial inunction with the prompter favorable action on symptoms, of rsphenamine
10. Notably useful symptomatically in late neurosyphilis.

all cases of late syphilis except cardiovascular and hepatic disease bismuth is now the proper opening treatment and arsphenamine should be temporarily postponed. Particularly is the drug serviceable in initiating the treatment of patients who for one reason or another impress one as clinically latent but in whom a complete investigation including study of the spinal fluid cannot be made at the outset. The rapidity of action of bismuth is such that a period of from two to six weeks constitutes an adequate preparation in the absence of definite lesions, which is materially shorter than that required for the slower acting intramuscular mercurials and mercury by inunction.

Bismuth is a valuable alternate in all cases of intolerance of or resistance to either arsenic r mercury Where arsenical by-effects in the skin have interfered with treatment, as in exfoliative dermatitis, bismuth becomes the next choice. On the other hand where the continued use of mercury threatens renal injury a rest period followed by the substitution of bismuth may do away with the difficulty Since the advent of bismuth it has become possible to treat with some semblance of efficiency the relatively rare cases of absolute

intolerance to all the arsphenamines. Bismuth preparations serve a particularly useful turn in the treatment of late neurosyphilis in which symptoms overshadow the serological findings. In the absence of the "red flag" syndrome or preparetic spinal fluid formula and in the presence of pain, paresthesias and degrees of symptomatic disability and emaciation in which for one reason or another an arsphenamine is contraindicated bismuth is superior to insoluble mercury or inunctions both on the score of absence of complications and positive therapeutic effects

In dealing with the latent case in which, after careful examination, only the necessity for maintaining the *status quo* becomes apparent, bismuth is again distinctly superior to mercury on the score of greater effectiveness and lower toxicity as well as a lessened likelihood of disturbing immunity balance through the use of the arsphenamines. None the less, in just such cases, regard for the waning but still significant worth of mercury calls for some division of the field between the two. In the treatment of late syphilis with trivial manifestations, as, for example, gummatous lesions in older individuals, mercury by mouth or inunction is particularly useful because of its relative freedom from reaction-producing qualities, its therapeutic efficiency and its relatively painless administration.

Bismuth Shortcomings.—The weaknesses of bismuth have been repeatedly referred to The tendency to trust too much to it on account of its spirillicidal and healing power is a very serious matter in modern practice and justifies sharp criticism of some of its proponents, particularly among manufacturers of pharmaceuticals Under no circumstances except those of an absolute intolerance should bismuth ever be used without an arsphenamine in the treatment of early syphilis, the practice of certain French authorities to the contrary notwithstanding (See Chapter XIV on treatment of early syphilis.) In the treatment of syphilis of the liver and the heart, allusion has already been made to very clear-cut intimations of significant and dangerous therapeutic shock effects.

MERCURY

Since the second edition of this work was published, mercury has definitely become syphilotherapeutic history Administered by mouth, it still gives faint favorable therapeutic push occasionally of use in old age and in the most ticklish and difficult of therapeutic shock situations. By inunction it is still useful in hospital practice, in isolated situations where patients must for months and even years, carry on a mild and safe treatment, free from risk of shock effect. We believe still that it is a safer approach to the more difficult, advanced and badly damaged cases of hepatic and cardiovascular involvement than the more popular bismuth. As a soluble mercurial salt it is still an effective spirillicide and an efficient agent in the treatment of certain forms of syphilis of the nervous system. As a colloidal preparation it can, with reasonable safety and good effect, be used intravenously For this degree of usefulness, extended consideration of the biochemical, toxicological and pharmacological action of mercurial preparations is not warranted despite the excellent work which has been done both in this country and abroad. This, with the history of the drug can be reviewed in previous editions of Modern Clinical Syphilology and in the articles by Lombolt, Rosenthal and Almkvist in the monumental Jadassohn Handbuch. Guided by the foregoing considerations, the discussion here will be purely clinical

Clinical Reactions to Mercury.—The clinically recognized toxic reactions to mercury include

1. Cutaneous manifestations, including fugitive erythema, scarlatiniform erythema (Billo, 1941), urticaria, diffuse and circumscribed edema and an acute vesicular dermatitis. Numerous other mercurial dermatoses have been described (Wright, 1930). Through secondary infection scattered inflammatory oozing crusted and infiltrated patches and plaques of wide distribution may develop. Purpuric manifestations are occasionally seen and a follicular papular eruption is recognized. The commonest and most vexatious mercurial cutaneous manifestation, however, is secondary to the irritation of inunctions, though intramuscularly injected mercurials may sometimes, even following the first administration, give rise to exfoliative dermatitis.

2. Mercurial stomatitis, probably the most common complication, is marked by more pronounced salivation than occurs with bismuth and by a less conspicuous tendency to pigmentation and discoloration of the gum margin. The lividity and edema of the mucous membranes due to the vasodilation, and the imprinting of the teeth indentations upon the margin of the tongue with an early tendency to the formation of leukocytic pellicles, are familiar characteristics. Fetor is pronounced but usually follows rather than precedes the development of marked stomatitis. The development of extensive necroses and tissue destruction suggesting Vincent's infection and agranulocytosis is less marked in our experience than with bismuth. Mercurial stomatitis is to an extraordinary degree amenable to the prophylactic control discussed under complications in Chapter IX.

3. Next in rank should be placed the gastro-intestinal reactions to the drug, conspicuous in mouth administration, often intractable and always to be avoided because once established they may constitute a permanent bar to the effective use of mercury in a given case. Mercurial diarrhea may follow suddenly on the injection of any intramuscular preparation and if a depot formation has developed may be so intractable that extreme degrees of emaciation and even death (as in the case of the gray oil) may ensue because the patient cannot be removed from the influence of the drug. Mercurial colic has been mentioned and may be an unmanageable contraindication to treatment. The abdominal pain may be so extreme that in combination with the meteorism frequently present it suggests intestinal obstruction or an acute abdomen. Gastro-intestinal complications, especially diarrhea, are favored by dietary irregularities, and especially by fruit and roughage, so that in the routine management of patients it is essential to inquire into and correct this point before concluding that mercury is not tolerated. Ulcerative colitis is a feature of severe mercurial intoxication.

4. Practically all mercurial therapy has a tendency to induce anemia through action on both the blood and bone marrow. While the drug has been called "the iron of syphilis," a certain degree of anemia is so universal a feature of effective therapeutic administration that the phrase bestows emphasis in the wrong place.

5. Mercurial rheumatism, the aches and pains, often with quite definite joint manifestations, associated with the intensive use of the drug, particularly by inunction, has its homologue in the bismuth grippe and may be so pronounced as to compel the suspension of the treatment.

Among the rarer manifestations should be included the effects of the drug on other mucous surfaces, including the induction of conjunctivitis, rhinitis,

intolerance to all the arsphenamines Bismuth preparations serve a particularly useful turn in the treatment of late neurosyphilis in which symptoms overshadow the serological findings. In the absence of the "red flag syndrome or preparetic spinal fluid formula and in the presence of pain, paresthesias and degrees of symptomatic disability and emaciation in which for one reason or another an arsphenamine is contraindicated, bismuth is superior to insoluble mercury or inunctions both on the score of absence of complications and positive therapeutic effects.

In dealing with the latent case in which after careful examination, only the necessity for maintaining the *status quo* becomes apparent, bismuth is again distinctly superior to mercury on the score of greater effectiveness and lower toxicity as well as a lessened likelihood of disturbing immunity balance through the use of the arsphenamines. None the less, in just such cases, regard for the waning but still significant worth of mercury calls for some division of the field between the two In the treatment of late syphilis with trivial manifestations, as for example, gummatous lesions in older individuals mercury by mouth or inunction is particularly useful because of its relative freedom from reaction producing qualities its therapeutic efficiency and its relatively painless administration.

Bismuth Shortcomings.—The weaknesses of bismuth have been repeatedly referred to The tendency to trust too much to it on account of its spirillicidal and healing power is a very serious matter in modern practice and justifies sharp criticism of some of its proponents, particularly among manufacturers of pharmaceuticals. Under no circumstances except those of an absolute intolerance should bismuth ever be used without an arsphenamine in the treatment of early syphilis, the practice of certain French authorities to the contrary notwithstanding. (See Chapter XIV on treatment of early syphilis.) In the treatment of syphilis of the liver and the heart, allusion has already been made to very clear-cut intimations of significant and dangerous therapeutic shock effects

MERCURY

Since the second edition of this work was published, mercury has definitely become syphilotherapeutic history Administered by mouth it still gives faint favorable therapeutic push, occasionally of use in old age and in the most ticklish and difficult of therapeutic shock situations By inunction it is still useful in hospital practice in isolated situations where patients must for months and even years, carry on a mild and safe treatment, free from risk of shock effect. We believe still that it is a safer approach to the more difficult, advanced and badly damaged cases of hepatic and cardiovascular involvement than the more popular bismuth. As a soluble mercurial salt it is still an effective spirillicide and an efficient agent in the treatment of certain forms of syphilis of the nervous system As a colloidal preparation it can with reasonable safety and good effect, be used intravenously For this degree of usefulness extended consideration of the biochemical, toxicological and pharmacological action of mercurial preparations is not warranted despite the excellent work which has been done both in this country and abroad. This with the history of the drug, can be reviewed in previous editions of Modern Clinical Syphilology and in the articles by Lombolt, Rosenthal and Almkvist in the monumental Jadassohn Handbuch Guided by the foregoing considerations the discussion here will be purely clinical.

reaction to treatment return t normal again if given sufficient time. Whether mercurial inunctions or intramuscular injections of mercury succinimide are given seems t make little difference in the time of ppearance or extent of renal irritation. The renal irritation resulting from combined arsphenamine and mercurial treatment is practically equivalent t the sum of that produced by the two drugs given separately Approximately one month is the proper time to allow for the urine to return t normal after stopping nonaccumulative mercurial treatment for syphilis. Patients with cord bladders under treatment for syphilis have very few casts in the urine, possibly due to disintegration but also perhaps to the fact that these patients kidneys seem less reactive than those of normal individuals and tolerate intensive treatment fairly ell. Patients who have damaged kidneys, as evidenced by chronic nephritis, nephrosis, focal nephritis and so forth show higher degree of reactivity t treatment than normal patients but recovery seems to be quite as satisfactory Reactions tend to become more severe as treatment progresses but if sufficient time for recuperation is allowed, repeated courses may be given, at least up to three or four without causing significant renal damage. Age as such is, moreover not contraindication to mercurial therapy from the standpoint of renal irritation. It is notable that spontaneous recovery from renal irritation may occur even in the face of continued administration of the drug, the kidney pparently acquiring tolerance

Mercury by Mouth.—Figure 81 is a thumbnail résumé in somewhat didactic form of the principle features of this mode of treatment.

Mercury by Inunction.—The inunction consists essentially of finely divided metallic mercury incorporated in a fatty base and rubbed into the skin, though at various times the substitution of insoluble salts such as calomel has been attempted in order to do away with the disagreeable color of the metallic preparation.

The distinctive qualities of the mercurial inunction are summarized in Fig 82.

The mode of absorption of the drug is via the respiratory tract secondarily and the skin primarily as shown by the studies of Welander and of Jenkins and Schamberg. The demonstration of globules of the drug in the skin about the hair follicles and sweat glands (Zwick) makes permissible the use of the so-called clean inunction in which the ointment remaining after vigorous rub is removed from the surface of the skin by fat-solvent such as benzine (Cole, Gericke, and Sollmann) Wile and Elliott have shown that mercury appears in the urine within twelve to twenty-four hours after its application to the skin. Saturation, however is slow according to Lomholt, and administration by mouth or preliminary intramuscular injection is permissible within the first tw weeks, which is as early as inunction therapeutic effects can be expected to develop Schamberg maintained that high proportions of calomel, over 50 per cent, may be used in inunctions effectively but Cole and Littman were unable to secure satisfactory evidence of its efficiency and most clinicians have discarded it.

The disadvantages of the inunction include particularly messiness, the possibility of betrayal a tendency to irritate sensitive skin and a ready onset of stomatitis if good mouth prophylaxis is neglected. Arsphenamine idiosyncrasy producing a tendency toward dermatitis, is a relative contraindication to the use of the inunction. Hairy patients develop intractable follicular irritation which may lead to mercurial dermatitis

Dosage Base Special Devices.—The official Unguentum hydrargyri (50 per cent metallic mercury) is satisfactory A tablet inunction of mercury in cocoa butter is cleaner and more easily rubbed in, and can be supplied in cakes containing 30 and 50 grains metallic mercury Measured dosage is extremely important and the infamous pea-sized inunction or amounts estimated as sufficient to go on a knife point, applied to the soles of the feet and small inconspicuous areas about the body have been responsible for much disappointment and disrepute for the inunction method. Four Gm. of the 50 per cent ointment weighed and dispensed in waxed paper or issued in capsules is the

average adult dose and 6 to 8 Gm. of the preparation (spoken of in case abstracts as "double-rubs) may be used in persons of large physique or for extremely intensive treatment.

The "course" of inunctions should rarely number less than forty taken at the rate of four to six rubs a week and more often the latter than the former The really extraordinary factor of safety in the mercurial inunction is testified to from an experience with more than 10 000 patients who have taken an aggregate of hundreds of thousands of rubs. Reasonably intelligent persons can be given as much as three courses of forty inunctions to be taken during the year and without other control than a careful instruction in mouth prophy-

Fig 82.

MERCURY BY INUNCTION IN SYPHILIS

1 The safest effective method of giving mercury but difficult to induce the patient to follow
2 The one really vailable method of effective self-medication in syphilis.
3. Valuable chiefly in institutional practice where its messiness is not objectionable, and in patients living alone
4 Avoids disturbance of the gastro-intestinal tract, but more readily induces salivation, hence insist on mouth prophylaxis.
5 The best tolerated of all mercurial treatment methods by the kidney
6. N cumulative effects.
7 Absorption is by the skin and respiratory tract.
8. A large area rubbed, energetic pplication, and warm room increase absorption.
9 Slow in getting into ction. T   eeks required for saturation.
10 Too slow for arsphenamine preparation in acut neurosyphilis and involvement of special sense organs.
11 Will not control contagious recurrence
12 Not sable on very hairy skins.
13 Provokes dermatitis in hypersensitive patients.
14 May precipitat a dermatitis in patients with arsphenamine idiosyncrasy
15 Overenergetic application favors complications.
16. T   hot baths nd sweat stop bsorption.
17 Underdosage is too often the rule One t 1½ drachms (4 to 6 Gm.) should be used with each inunction.
18. Use the 33 per cent strength of mercurial ointment when combined with arsphenamine If desired, 8 Gm. can be used. Fifty per cent strength is widely used.
19 Give rubs in courses of 40 t 80 six each week, with rest intervals of one t two months bet een courses. Three hundred is good total in early syphilis
20. Substitutes for metallic mercury in inunctions (calomel, etc.) are not gaining acceptance. Mercury oleate inunctions (15 Gm. of an ointment containing 1 Gm. mercury oleate) may be the exception (Sollmann *et al.*, 1935) These inunctions also have the advantage over metallic mercury of cleanliness, lack of detection, and greater ease of inunction.

laxis and occasional examinations of the urine can carry on their own treatment in conditions of relative poverty and isolation with a minimum of expense and with good therapeutic results as gauged by modern standards. Explicit directions to the patient go far to promote the effective use of the mercurial inunction and for that reason the instructions for taking rubs which are given in printed form to our patients are here reproduced verbatim (Fig 83) The clean inunction as devised by Cole Gericke and Sollmann differs from the general instructions in that the rubbing is carried out for thirty minutes by the clock, the area rubbed is at least eighteen inches in diameter the e cess ointment is wiped off with a soft cloth and the grayish stain on the kin re-

moved with a cotton pledget moistened with soap and water. The patient is permitted to change underwear and bedding whenever he desires, and to bathe. Absorption is from the follicles and the globules which have penetrated into the upper layers of the cutis. The fluidity of the mercurial globules is evidently important for pressing them into the follicles (Sollmann, Cole and Schreiber 1935). Cole, Rauschkolb, Schreiber and Sollmann have shown by careful elimination studies that it is possible to give mercury by massive

Fig. 83.

INSTRUCTIONS FOR TAKING "RUBS"

The medicine used in taking rubs enters the body through the skin. It must never be taken by mouth, or placed where children can reach it.

Rubs are taken in sets of six, one rub every night and a bath in place of a rub on the seventh night. Before rubbing, the skin where the rub is to be taken is to be thoroughly washed with soap and water and dried with alcohol intended for use on the skin. The rub is taken on one of six different places, a different place being used each night. The room in which the rub is taken should be warm.

1. The first rub is taken on the right-hand side of the chest in front of and below the armpit.

2. The second rub is taken on the left-hand side of the chest, in front of and below the armpit.

3. The third rub is taken on the right-hand side of the abdomen or on the flank.

4. The fourth rub is given on the left-hand side of the abdomen or on the flank.

If there is any hair on the outside of the thighs, the fifth or sixth rubs can usually be taken on the insides of the right and left thighs, respectively. Be careful not to rub where there is hair and do not rub two nights in succession on the same spot. If you are giving the rub to someone else, the back may be used for two or more rubs. Do not rub where there is hair or the skin will become inflamed. If there is much hair on the body call your physician's attention to it and ask him to tell you where to rub. Rub for at least twenty minutes *by the clock*. Rub firmly but not roughly. The skin should not be sore after the rub. Rub in a space of about a foot or 16 inches in diameter. Wipe off any ointment which remains on your hand on to the skin when you have finished.

Powder the skin after rubbing if you wish, but do not attempt to wash off or remove any of the ointment.

Through the entire series of six rubs the patient *should wear the same suit of underwear*. It is better to use old underwear which will become stained with the ointment. *Don't bathe during the series of six rubs* without special permission from your physician. After completing the series of six rubs, a bath should be taken on the seventh night in place of a rub. This bath should be with soap and hot water and all the grayish stain from the rubbings should be removed from the skin. The skin should then be powdered and the patient must change the underwear.

Rubs are usually given in sets of six and *the course of rubs consists of not less than forty*, covering a period of six or seven weeks. During such a course it is important that you should see your physician once in two weeks unless he allows a longer interval. Do not allow yourself to miss or skip rubs during a course without your physician's permission.

While this form of treatment is not pleasant, it is very effective and will do you much more good than the taking of pills or other medicine by mouth. For that reason you should persist in it as long as your physician thinks necessary, even though you may have to take a number of courses. Be sure to report to your doctor any trouble with the mouth or teeth. Your urine should be examined by a physician at least once in two weeks.

weekly inunctions to the body with 30 Gm. of the mild mercurial ointment U.S.P. without ill effects to the skin or other significant complications. A greater and more rapid cumulative excretion of mercury in the urine and an equal fecal output ensues, as compared with other methods of administration. The ointment was applied by two rubbers working for sixty minutes on each patient, and covering especially the chest, thighs, and forearms.

Belt Method.—Special methods for giving the inunction may be practiced in institutions, usually with the aid of masseurs. They are very effective in experienced hands. A belt for the

continuous administration of mercurial ointment percutaneously has been described by Wenge and its effectiveness under conditions involved in camps, penal practice and so forth, demonstrated. The belt is of rubber material 15 ½ inches, with a 3 ½ inch elastic tab t each end t permit fastening and freedom of movement. The belt is worn throughout the day carrying the day dose of mercurial ointment, and in the course of several hours the da dose is absorbed without interruption of the patient working activity The lif of the belt is between three and four months and the degree of bsorption secured is said t be efficacious nd t be demonstrated by the usual symptoms of mercurial saturation. Inquiries may be addressed t the Division of Venereal Diseases, U S Public Health Service Bethesda Station, W shington, D C.

MERCURY BY INTRAMUSCULAR INJECTION

The soluble salts of mercury in common use for intramuscular injection are the bichloride the succinimide and the benzoate. The insoluble preparations most widely used are mercuric salicylate the red mercuric iodide calomel metallic mercury finely divided in oil commonly spoken of as the "grav oil (Oleum cinereum) and certain colloidal preparations of mercury including most recently colloidal mercury sulphide.

Soluble Mercurial Salts.—Soluble mercurial salts are usually administered in aqueous or saline solution Their absorption is rapid and the therapeutic action of the simpler salts is prompt and noncumulative for relatively little of the drug is fixed as such in the injection site The use of glucose solution as a medium has recently been tried with apparently good results The incorporation of water-soluble mercurials in oily or fatty vehicles, precisely as in the case of bismuth markedly delays their absorption and reduces their effectiveness In order to secure good results from a soluble mercurial salt in aqueous solution, the injections must be given frequently daily or every second day and practically never less than once in three days. The injections have the reputation of being more painful than those of insoluble salts, but reaction is shorter-lived if more acute and is often a function of the salt used the concentration and the technic, rather than an intrinsic disadvantage in the method Under the competition of bismuth the soluble mercurial salts remain the only ones with the possible exception of colloidal mercury sulphide which the inexperienced practitioner can use with comparative safety to the patient and assurance of satisfactory and rapid effect. The soluble mercurial salt, as Lier noted a number of years ago, will dispose of infectious recurrences which have developed in the very midst of a course of inunctions or insoluble injections. The prolonged renal irritation and the gradual decline in vigor which patients treated with insoluble mercurial salts too often exhibit, we have practically never seen with a soluble salt. On the other hand there can be no denying the inconvenience of the daily injection and some patients are not so situated as to be able to accept it

Dosage, etc.—The bichloride of mercury and the succinimide are used in doses from ⅙ to ⅛ grain, four to six times weekly The solution can be made up in distilled water or physiologic saline in 30 cc quantities, kept in dark glass stoppered bottles 1 cc. of the solution representing the proper dose Larger quantities should not be made up at one time. The solutions are self sterilizing The succinimide is now marketed in this country in ampule form, with or without a local anesthetic such as butyn, and is very easily given, with almost no local reactions. The dosage of the red mercuric iodide and that of the benzoate is also ⅙ to ⅛ grain, three to five times weekly

A warning should be issued against the use of other tha glass containers for soluble mercurial salts. In dealing ith soluble mercurial salt it is also necessary t bear in mind the striking

and t times quit unaccountable variations in the behavior of different lots of supposedly pure soluble salts, which must be due t unknown chemical variations in composition or the presence of impurities.

Colloidal Mercurials.—The colloidal mercurials range all the w y from glucose suspensions of finely divided mercury which settle out on standing to the true colloid, such as the sulphide prepared and investigated in this country by Hille Wakerlin, reporting on the effectiveness of this drug in experimental animals, was very favorably impressed with it and Freeman, T ylor and White, using the drug in 25,000 injections in man, commented especially upon its serological good effects and its freedom from reaction. Lawless rates the drug as very effective mercurial by the intravenous rout especially albeit with definite renal toxicity

MERCURY ADMINISTERED INTRAVENOUSLY

Mercurial preparations can be administered intravenously as Baccelli demonstrated in 1893 and the fact that there is no corresponding safe route for the intravenous administration of bismuth will perhaps perpetuate for a time this otherwise unnecessary and esoteric method of using the drug

I cases in which it is considered absolutely essential t use mercury intravenously the oxy cyanide as the most familiar salt, is probably the best one to employ administered on dosage scale of 0.2 mg per kilo, or 12 mg. for the average adult dose.

Colloidal mercury sulphide introduced by Hille is stabilized in colloidal solution by hydrolized protein nd according to Gennerich is well tolerated when given intravenously and exerts surpassing mercurial action. It is especially effective against the positive W ssermann reaction but its clinical action is definitely inferior t the arsenicals. This drug is given in dosage of 2 to 3 cc. twice eek and may be safely administered continuously for series of 30 to 60 injections. Care must be exerted to void extravascular deposition of the drug, which produces lasting pigmentation of the skin.

The Action of Mercury on Syphilids.—The disappearance of spirochetes from primary and secondary syphilids treated with various mercurials varies from forty-eight hours to more than thirty-one days. (Ingraham, 1937) Given by mouth the rate of involution of the primary lesion and of secondary eruptions is only a little faster than their spontaneous resolution in the course of the disease Late manifestations, especially when iodide is given simultaneously sometimes respond with extraordinary rapidity considering the mildness of the measures employed. A rather extensive gumma of the forehead, for example, may disappear in three to six weeks. Mercury by inunction in spite of its greater intensity sometimes does not seem to secure more rapid healing effect than mixed treatment by mouth, so far as external lesions are concerned. There is a lag of at least two weeks in most cases before the beginnings of a real mercurial effect can be seen under inunction treatment. The soluble mercurial salts such as the succinimide however give rise to very rapid responses, a severe and extensive neuroretinitis, for example with hemorrhage and exudate, involuting completely in the course of fifteen to twenty daily injections, a rate hardly to be exceeded by bismuth or the arsphenamines. Similarly condylomatous lesions at the anus can be made to disappear in from seven to fifteen days the organisms vanishing before the fifth or sixth day Five to six weeks must be allowed for the resolution of a palmar syphilid under that most potent mercurial, the gray oil or calomel intramuscularly

Nonspecific Effects of Mercury—The use of blue ointment as inunction for the local treatment of periosteal lesions in bone has been familiar orthopedic practice Choroiditis of nonspecific origin will respond to mercury succinimide almost as rapidly t times, as t an arsphenamine. Even lupus vulgaris of the ulcerative type will mak some degree of improvement under

soluble mercurial salt and the mycoses and other granulomatous processes likewise at times show striking responses. On the other hand, in our experience, tuberculids, particularly the papulonecrotic type, d not d ell under mercury possibly because of its unfavorable effect in stirring up focal infections especially about the mouth and teeth. The nonspecific action of mercury with chalk by mouth is pronounced in such conditions as rosacea, which are associated with marked abnormalities of intestinal flora and hence improve under local antiputrefactive drugs. Mercury with chalk, for instance, is valuable in pruritus ani, very possibly for this same reason—namely its elimination at the seat of chronic infection. Mercury protiodide by mouth has been said by Whit Fox and others t influence favorably the course of verruca plana or flat warts.

Therapeutic Shock and Paradox.—The original observations of the Jarisch Herxheimer phenomenon were of course made on patients receiving mercury intramuscularly It is therefore apparent that it shares with arsphenamine and bismuth the ability to induce therapeutic shock. For this reason all initial dosage of mercurials should be reduced both to determine the tolerance of the patient for the drug and to avoid local flare-ups On the other hand the local shock effect is trifling with mercury as compared with arsphenamine and bismuth and this makes the drug under suitable conditions of dosage the *ideal* one for the introduction of treatment when shock effects are to be avoided. Mercury by inunction in particular is the most serviceable mode of administration where anything suggesting a Herxheimer effect must be avoided. The technic of preparation with heavy metal to avoid arsphenamine therapeutic shock effects will be presently discussed.

Other Heavy Metals

Extensive investigations conducted by Levaditi and Nicolau and their coworkers, including Fournier and Guénot, by Versari, by Proescher Seil, and Stilliams, by Jahnel (1928), by Klauder Vignati and Beinhauer and Jacob, have finally clarified quit definitely the question of the value of other metals chemically related to arsenic and bismuth in the treatment of experimental and human syphilis. The situation may be summarized by saying that mercury bismuth, tellurium, vanadium, platinum and gold are the only metals now definitely known to have antisyphilitic action.

N appreciator of the history of syphilis ould feel content with presentation of non specific therapy that did not mention the famous Zittmann decoction. This formula has sustained number of modifications, the basis of all of which is sarsaparilla. Perutz rates this one of the nonspecific modes of treating the disease comparable t the action of nonspecific protein and other forms of Reiz or shock therapy The active principle seems to be saponin in both this and the guaiac therapy

The Iodides

Historical Considerations.—Martin of Lubeck is credited ith the first administration of iodine in 1821 in the form of burnt sponge for the treatment of venereal ulcers of the throat The potassium salt as first employed by Wallace of Dublin in 1834 and it indications and contraindications pointed out. It has always been favorite with the French school of syphilologists and ttained under their influence recognized place in the treatment of the disease which in the American offshoot of French syphilology has amounted t perhaps at times an exaggeration of its importance in the treatment of the disease. Of lat German revival of nonspecific therapy for syphilis has brought various iodide derivatives t the front in the literature

The action of iodides is more completely nonspecific than that of any other commonly used standard medicament in syphilis. Nichols showed that in tolerated doses the drug has no spirillicidal action. It does not apparently influence the blood Wassermann reaction to any definable extent, but it does *assist materially in the resolution of granulomatous tissue* Pearce finds evidence of beneficial effect on systemic syphilis in the rabbit, especially when given in small doses over a long period of time

The action of the iodine radicle in the body is evidently matter of much complexity and it remains to be seen whether its influence on the metabolism as controlled by the thyroid gland, and thus on the general resistance of the patient t infection, has any special bearing on the action of the drug in syphilis. The theory of Jobling and Peterson, while not perhaps fully confirmed as yet, offers the best combined explanation of the local and systemic effects of the drug. These authors consider that the iodine radicle combines ith the unsaturated lipoids of the blood and tissues, thus inhibiting the action of the ntitryptic or antiproteolytic ferments which nor mally prevent utolysis. This inhibition of ntiferment permits the digestion of the tissues in which it occurs, with the disappearance of the digested tissue and its replacement by scar The selection of diseased tissue as site of deposit for unusual amounts of the iodine introduced is responsible for the seemingly specific selective action on granuloma, and is chemically demonstrable according t these uthors, in both tuberculosis and syphilis.

Inasmuch as iodides exert no spirillicidal action and do not, like mercury stimulate a specific cellular resistance mechanism against *Spirochaeta pallida*, they remain merely an adjunct to treatment, whose value is undoubted but also somewhat undefined.

Iodine is administered conventionally in the form of the iodides of sodium or of potassium. Small amounts of the drug may be introduced by inunction in oily bases, but no advantages are apparent to compensate for the smallness of the dose Certain organic iodine preparations (e g Siomine N.N.R.) are sometimes useful in patients intolerant of the inorganic iodides. Both sodium and potassium salts are rapidly absorbed when administered by mouth or rectum, and the sodium salt may be given intravenously in large doses though this mode of administration, like iodide therapy in general has been largely displaced by other more directly efficient methods

The following summary of the pharmacology of the iodides is abstracted from the extensive ork of E. D Osborne (1922).

Ninety-six per cent of iodine ingested is bsorbed from the gastrointestinal tract regardless of the dose (up to 20 Gm.) Within ninety-six hours practically the entire amount is liminated, also regardless of the dose, so that there is no evidence of cumulative action on the part of the iodides, as distinguished from mercury or the arsphenamines. Practically the entire amount of iodine administered, regardless of the route is eliminated through the kidneys, negligible quantities appearing in the stool even after diarrhea following very large doses. There is no evidence that the amount of urine excreted influences the amount of iodine excreted, and there are no urinary signs of iodine irritation. There is no difference between the rat of elimination when the drugs are given before or after meals, and, in fact, Osborne advises administration thirty minutes before meals because of the diminished gastric irritation. There appears also to be no advantage in the coincident administration of fats such as milk.

There is no advantage in administering small doses (2 to 5 Gm.) of sodium iodide intravenously unless the drug is given simultaneously by mouth.

A dose of 5 Gm of either sodium or potassium iodide three times day by mouth will maintain concentration of 20 to 40 mg. of iodine for each 100 cc. of blood serum for ten to twelve hours. This is equivalent to the concentration maintained for short time by 10 Gm. daily of sodium iodide intravenously thus being the average tolerated adult dose for the intravenous route. The iodine content of the blood serum following the intravenous injection of 10 Gm. of sodium iodide in 10 per cent solution rises to peak of 45 mg. per 100 cc. t the end of the first hour and drops rapidly until at the end of twenty-four hours it has fallen to 7 mg.

The concentration of iodine in the spinal fluid, of interest in the treatment of neurosyphilis, was likewise studied by Osborne. The issue is, of course, of special importance with reference to the securing of better penetration of the meninges by the drug following intravenous as contrasted with mouth or rectal administration. Osborne, working with sodium iodide, showed that while there was distinct variation in different individuals, and markedly greater increase in concentration in patients with active meningeal neurosyphilis, there was in general definite superiority in intravenous injection as compared ith other routes, in increasing the iodine content of the spinal fluid. There were also indications that neurosyphilitic tissue takes up more iodine than normal tissue in the nervous system. The curve of excretion from the spinal fluid parallels that in the blood

Clinically we may say that sodium iodide by mouth is regarded as less effective and is likewise less irritating to the gastro-intestinal tract than potassium iodide by the same route. The physiologic basis for this has been demonstrated by Osborne It is, however definitely better tolerated by mouth than potassium iodide in patients who show an idiosyncrasy Rectal administration is practically superfluous except in rare instances in which intravenous iodide is not available and mouth administration impossible The intravenous administration of sodium iodide is often well borne by patients who are subject to gastro-intestinal reaction. It is a method for securing a high concentration of the drug in the blood-stream for a short time and for

Fig. 81.

THE THERAPEUTIC USE OF IODIDE IN SYPHILIS

1 Highly nonspecific. Do not use for therapeutic tests.
2 A resolver of granulomatous processes.
3. A stimulator of resistance in prolonged small-dose administration.
4 The familiar concomitant and synergist of mercury
5. Useful where early syphilids, including the indurated chancre resist treatment.
6. Appropriate in large doses in all active neurosyphilis, including early symptomatic, diffuse, meningeal, meningovascular vascular and gummatous lesions.
7 Most useful in moderate doses in visceral syphilis.
8. Valuable in all forms of syphilitic cardiovascular disease small to moderate doses.
9 Effective in small doses in cutaneous late syphilis.
10 Use in prenatal syphilis as in late acquired syphilis.
11. Useless in syphilis of the pregnant woman for protection of the child.
12. Excellent interim treatment between other courses in serologically resistant cases.
13. Advocated for "loosening up" entrenched processes.
14 Small doses, 5 to 15 grains daily; moderate doses, 30 to 100 grains daily large doses, 150 to 1800 grains daily
15. Intravenous injection of sodium iodide may be useful in neurosyphilis; seldom required elsewhere Give 30 to 150 grains (2 to 10 Gm.) per dose, 3 to 5 times a week in addition to iodide by mouth.

Iodide ought not to be a stop-gap; it is not a spirillicide it is not specific. Yet, if no contra-indication appears, and in doubt whether to give it or not, better give it.

securing a maximum penetration of the nervous system. It should not be used for the administration of small doses (less than 7 to 10 Gm daily) potassium iodide by mouth producing as good results.

Toxicology of Iodides.—Iodides have in general so low a toxicity that there need be no fear of damage to vital structures by their intensive use in the overwhelming majority of cases. In fact the tolerated dose even in clinical practice is unbelievably large reaching at times in the therapy of blastomycosis 1500 grains a day On the other hand it is never possible to predict when iodide idiosyncrasy of a grave type may be encountered so that it is wise to make the first dose given a small one as Col. Harrison points out (*i. e.*, 5 grains) The recognized reactions include the syndrome of "iodism" including a catarrh of the mucous membranes in mild cases, and severe edema of the larynx in critical cases gastro-intestinal disturbances ranging from a brassy taste in the mouth produced by the excretion of the drug in the saliva, to anorexia nausea vomiting intestinal cramps and diarrhea iodide "mumps" an aching sensation at the angles of the jaw (Moore) and cutaneous reactions, including iodide acne erythema multiforme angioneurotic edema fungous,

vegetative, and frambesiform eruptions (Fig 85) acute bullous iodism and exfoliative dermatitis similar to that produced by arsphenamine and occasionally by mercury Recently febrile reactions, sometimes severe, have been reported following the use of iodides (Katzenstein 1938, Barker and Wood 1940) Stewart and Smith (1941) demonstrated changes in the electrocardiogram and in the cardiac rhythm during the therapeutic use of potassium salts and they advise careful supervision in the use of potassium iodide in the treatment of syphilis if toxic effects on the heart are to be recognized and avoided

Underlying all these reactions except the gastro-intestinal is a definite strain of idiosyncrasy which suggests some decided change in the colloidal balance of the tissues of susceptible persons. Bruck early investigated the mechanism of iodide idiosyncrasy and believed that he had demonstrated its transmissibility t animals through the medium of the serum, parenterally injected,



Fig. 85.—Frambesiform and vegetative type of iodide eruption.

of the susceptible person, but critical analysis of the work in the light of better modern conceptions of anaphylaxis and sensitivity lays its authenticity open to question. Wile, Wright, and Smith conclude that bacteria are not the sole cause of iodide and bromide eruptions, and that these eruptions cannot be classified as true sensitization phenomena as yet.

There is, of course, striking resemblance between certain of the cutaneous eruptions of iodism and those of bromism, in which the irritative effect of the drug perhaps lays the tissues open to the action of pyogenic micro-organisms. This may explain the bromide and iodide acnes and the fungoid and frambesiform lesions, but the fulminating erythema and edema that come on acutely after an intravenous injection, and the angioneurotic edema partake more of the character of vascular injuries Acute bullous iodism, fortunately very rare, is fulminating and fatal complication, with enormous bullous lesions appearing on base suggestive of an erythema multiforme with purpura. The exfoliative dermatitis of iodine idiosyncrasy may come on following the external application of iodine for disinfection or the use of iodoform, but we have never seen it follow the internal administration of iodides either by mouth or intravenously

There is an interesting difference between the effect of small and of large doses of iodides, which deserves experimental study Small doses seem more likely to give rise to coryza and acne than large doses. It has been not uncommon experience with the drug to see all signs of an annoying iodism disappear after the dosage passed 30 grains t. i. d by mouth. Patients who start with 30 grains seem less likely to develop signs of idiosyncrasy than those who start with 5 grains.

On the other hand, some patients develop gastro-intestinal intolerance on the higher doses, illustrating the difference between a sensitization and purely local irritative reaction.

Iodide by Mouth.—The potassium salt is in general the more satisfactory Two schools of therapy exist with reference to the dosage to be used. One group defends the small dose of 5 to 10 grains t. i. d., and the other advises a dosage of from 25 to 100 grains t. i. d or more. There is no experimental basis for either viewpoint as yet, beyond Pearce's observation of the resistance-stimulating effect of small doses in rabbits and the increase in iodine content of the blood with increasing doses observed by Osborne Clinically small doses of iodide seem able to hasten the resolution of syphilitic granulomata in the skin and bones almost as well as large doses. On the other hand, in such granulomas as that of blastomycosis the larger the dose, the better the effect. In the treatment of actinomycosis very large doses sometimes seem less effective than moderate doses. We have personally inclined in treating neurosyphilis to a dosage of 25 to 100 grains of potassium iodide three times a day The dose is usually made ascending, in the belief that there is an increase in tolerance thus obtained. A 1 1 aqueous solution in distilled water should be used (not a saturated solution) so that 1 minim equals 1 grain of the drug, and measurement with a minim glass or a dropper is usually desirable. The solution turns brown on exposure to light (free iodine) but is not necessarily spoiled. It should be kept in a dark place If difficulty is persistently experienced in attempting to use smaller ascending doses, an abrupt jump to 30 or 40 grains t. i. d. may overcome the idiosyncrasy Dosage may be increased by 1 to 5 grains daily thus meaning as must be carefully explained to patients, that each day's increase is to be taken three times during the day not added on to each succeeding dose. When the maximum is reached the dose should be held at that point until the necessary amount is taken, not decreased gradually to the starting point. Dilution markedly increases the tolerance of the iodides and doses of 50 grains should never be taken in less than a glass of water 100 grains in 2 glasses, 150 grains in 3 glasses. Milk is unnecessary except in infancy and childhood. The drug should be taken *before* and not after meals, to favor its early escape from the stomach. In patients who are markedly intolerant of iodide by mouth it is at times possible to give very large doses by putting the entire amount for the day in a gallon and a half of water and having the patient drink it in lieu of other beverage during the day Col. Harrison suggests the taking of the day's allotment in a single dose as effective For the brassy taste in the mouth little can be done but most patients soon grow accustomed to it. Rinsing the mouth with an aromatic wash (liq antisepticus alkalinus) just after taking the dose and before eating helps some patients to forget the annoyance Patients who have a marked gastric intolerance can often take sodium iodide intravenously without reaction. This is *not* true of patients with marked iodism and idiosyncrasy however The iodide eruptions should be watched for and the drug discontinued if any signs of the more serious types appear The acne often responds to a reduction of carbohydrates in the diet and the use locally of Lotio alba. The involution of fungoid iodide lesions may be hastened by wet dressings of potassium permanganate An attempt to demonstrate a specific cutaneous sensitively in one case of this type was successful controls of sodium bromide and sodium chloride solution being negative. It should be remembered that nursing women excrete iodide in the milk and that the child may therefore react sometimes violently

Sodium Iodide Intravenously.—With the development of fever therapy and fever-chemotherapy sodium iodide intravenously has ceased to be an important item in the treatment of neurosyphilis. To save space the description of its use, which involves a number of significant technical points, is omitted from this edition. A 10 per cent solution in distilled water sterilized by boiling for ten minutes and administered with every precaution employed in the use of the arsphenamines is the basis for the technic. The maximum dose is ten Gm. once a day. Its use should be preceded by a two-day tolerance test of the drug by mouth, 20 grains of potassium iodide t. i. d.

Contraindications to Iodide.—One definite contraindication to the indiscriminate use of iodide in the treatment of syphilis in addition to idiosyncrasy must be borne in mind. The drug should not be given to patients with thyroid adenomas. We have seen several serious examples of adenomas being made toxic in this way. Tuberculosis is a conventionally accepted contraindication. Iodide is sometimes blamed for serious acute edema in laryngeal disease and Henck advises against it in nephritis with concentrated urine. Klauder and Vandoren (1941) believe that the iodides unfavorably influence the final visual acuity in both active and inactive interstitial keratitis.

The Technic of Heavy Metal Preparatory Treatment

The Importance of Preparation.—The technic of heavy metal preparatory treatment for the avoidance of therapeutic shock will be repeatedly referred to in subsequent chapters. It is therefore here described and merely referred to again under the prevention of complications. The fresher the infection, the younger and more robust the patient, and the more clearly it can be demonstrated by careful and complete examination, including serological tests of the spinal fluid, that no critical form of involvement or disease of a vital structure exists, the less necessary is preparatory treatment for the use of the arsphenamines. On the other hand, so rarely are these conditions fulfilled in average clinical practice, especially in latent and late phases of the disease, and so difficult is it with the relatively coarse methods available in most medical examinations to detect minute but extremely important foci that preparatory treatment is justifiably important in the protection of the patient against that large group of complications classifiable under therapeutic shock or Herxheimer effect. The use of the heavy metals because of their slower action as compared with the arsphenamines is not an absolute necessity, for increasing exploration of the field of small-dosage arsphenamine therapy tends to indicate as in the Kothny Müller Deham technic for treating cardiovascular syphilis and our own experience with bismuth arsphenamine sulphonate (bismarsen) that minute ascending dosage of an arsenical can be made to take the place of the preliminary use of a heavy metal to a considerable extent. None the less, the physician called upon to treat syphilis with the knowledge of the present day will, we believe, feel safer if he adopts the general rule of limiting initial vigorous use of the arsphenamines to early syphilis and with the aid of bismuth protecting his patients from unpredictable explosive and destructive effects by preliminary heavy-metal treatment.

Preparatory Treatment in Early Syphilis.—Early in the course of a syphilitic infection, that is, within the first several weeks, warnings of risk of serious complications may be drawn from a history of severe or violent headaches or of visual or eighth nerve disturbances, particularly tinnitus and dizziness or jaundice. If any of these symptoms be definitely present, it is wiser to begin

the treatment of the patient with bismuth rather than arsphenamine postponing the latter drug until the symptoms are abated or investigation discloses their lack of significance for the disease. Often a spinal fluid examination may be necessary to establish this fact. After three to six weeks of bismuth therapy the patient may usually safely be placed upon an arsphenamine. If the symptoms, as for example, of a fulminating papillitis or neuroretinitis, are actually endangering the patient's vision, much more rapid effect can be secured by the daily injection of ⅙ to ¼ grain (0.01–0.016 Gm.) mercuric succinimide accompanied by large doses of iodide. This method of preparation is also usable in less pressing but definite complications originating in the nervous system. It need not usually be continued longer than two to four weeks, following which an arsphenamine may be employed. These statements should not be taken as authority for the neglect of the intensive use of arsphenamine in all phases of early syphilis in which no definite danger signs appear and care must be taken not to overestimate trifling complaints as an excuse for evading an intensive beginning of treatment for curative effect.

Preparatory Treatment in Late Syphilis.—In the later phases of the disease especially where it has been impossible to make a thoroughgoing examination, three forms of preparation are useful including (*a*) bismuth intramuscularly (*b*) mercurial inunctions (*c*) a soluble mercurial salt such as the succinimide intramuscularly. If anything approaching a rule of thumb may be proposed 20 to 30 injections of mercuric succinimide ⅙ to ¼ grain (0.01–0.016 Gm.) with liberal doses of iodide by mouth (50 to 100 grains t. i. d.) or sodium iodide intravenously constitutes the preferred treatment, when obtainable, for an acute neurosyphilis. Failing this, bismuth sodium tartrate may be given in doses of 2 cc. twice or even three times weekly but this alternative we regard as distinctly second best. Bismuth preparation in late syphilis with incomplete examination may be made with any one of the effective liposoluble salts or the oil-suspended bismuth salicylate four to twelve weeks being required under ordinary circumstances. In cardiovascular syphilis extremely small doses of bismuth or of bismuth arsphenamine sulphonate (bismarsen) not exceeding 5 mg. bismuth metal for the first several doses or 10 to 25 mg. of the bismuth arsphenamine sulphonate makes an excellent approach to more intensive treatment. In late hepatic syphilis, the mercurial inunction with moderate doses of iodide by mouth is still unsurpassed and patients should be urged to take this form of treatment from four weeks to three *months or even a year before an arsenical is considered.* *Observation of a* number of unfortunate and even disastrous end-results of haste and fast acting drugs in hepatic and cardiovascular syphilis have led us to return almost with enthusiasm to mercury and iodide. Even the initial administration of mercury by mouth may be necessary in properly grading the approach to more intensive treatment in syphilitic hepatic cirrhosis. These strictures placed upon the use of intensive modern methods in late syphilis should not, as has already been said, be allowed to veil or overshadow the tremendous importance of the initial use of the arsenicals in early syphilis in the absence of clear-cut contraindications. But just as a system for treatment to be used in early cases of syphilis should emphasize and depend on the arsenicals as a public health as well as therapeutic ideal so the system in late cases taught the average medical student must subordinate and defer the use of arsenicals since there is no infectiousness to control, in favor of the slower, safer preparatory treatment with bismuth or a mercurial.

CHAPTER VII

THE ARSENICALS—THEORETICAL AND PRACTICAL CONSIDERATIONS

The Field of Arsenotherapy.—"Arsenic" has come to imply a species of art-magic in the mind of the medical profession whenever the therapy of syphilis is considered so that the first word of a discussion of the arsenical phase of treatment must be one of caution. The combinations in which arsenic is involved in the chemotherapy of syphilis are fully as important to the behavior of a drug which contains it as is the arsenic radicle itself. Moreover the valence of the arsenic is of the greatest importance and trivalent as distinguished from pentavalent arsenic is essential to the spirillicidal action of the arsenicals used in the treatment of syphilis. Trivalent arsenic has dominated the scene since 1910 but the growing importance of the pentavalent group merits extended discussion. Into the development of the trivalent arsenicals is crowded one of the fascinating romances of medical history and both for its perspective-giving value in a comprehension of this enormously important group of drugs as well as for its worth as an exemplar of human progress an historical summary seems in order.

The Trivalent Arsenicals—Historical Considerations.—The arsphenamines which constitute the outstanding modern representative of the group of trivalent arsenicals are the products of dye chemistry fired by the genius of Ehrlich—a biologist who well illustrates how great men are so often made by combinations of aptitude and circumstance. A lifelong familiarity with the processes of body metabolism and particularly with the oxidation-reduction chemistry of living cells combined in him with an acquaintance with the chemistry of dyes and a coincident knowledge of parasitology to provide the foundation for an extraordinary theoretical vision. As a piece of constructive thinking, the synthesis of the arsphenamines is an astonishing and epochal achievement. To it, however, as to most great consummations, many men contributed. Laveran and Mesnil, through their studies of the *Trypanosoma equiperum* and their development of a controllable mouse technic, contributed the organism that was to form the base for the chemotherapeutic contact with disease. Shiga, and Von Weinberg, working with Ehrlich, identified the first trypanocidal effect of a dye of the benzopurpurin group, and took the first step in rational synthesis by introducing sulphogroups into the compound to form a soluble product with markedly increased trypanocidal effects. This was the dye Trypan Red with which modern trypanocidal chemotherapy began. Laveran and Mesnil introduced arsenic into the problem. Atoxyl, the first chemotherapeutic compound to receive extended trial in man, only to be subsequently abandoned because of its relatively frequent induction of optic atrophy, came on the stage with the work of Béchamp (1863) and later of Landsberger and Blumenthal. The efforts of Thomas and of Breinl and Kinghorn to apply atoxyl to human trypanosomiasis therapy attracted Ehrlich's attention to the drug and Uhlenhuth, Gross and Bickel showed it to be active against the spirochetosis of hens. Thereupon Ehrlich, working with the chemist Bertheim in a lifelong association which led directly to the synthesis of the arsphenamines, treated atoxyl with nitrous acid, obtaining a diazo-like dye-forming compound that upset all previous notions of the constitution of atoxyl and provided the key to the future chemistry of the arsphenamines in the so-called arsanilic acid. By successive steps the panorama was unrolled; the vital importance of the amino group in further synthesis was demonstrated together with the recognition of the body's intervention in the production of parasiticidal action by reduction of pentavalent to trivalent arsenic, a process that does not occur in the test tube. These genuinely inspirational conceptions were the direct outcome of previous unrelated studies by Ehrlich of the oxygen requirements of the body. Ehrlich

concluded as his experience increased that to secure maximum spirillicidal efficiency the reduction must be performed for the body not by it.

Next, utilizing an observation from his experience with azo dyes, Ehrlich grasped the importance of the ortho position of hydroxyl and amino groups in producing trypanocidal drugs. The aminophenylarsenic acids followed and then by another reduction with sodium hydrosulphite, the arsphenamine base and its dihydrochloride the 606th of a series of compounds elaborated by Ehrlich and his coworkers. The halogen plays an essential rôle even in this drug, so generally thought and spoken of by the physicians who use it and its derivatives, as "arsenic.

The intricacy of the intramolecular chemistry of these dyes is illustrated by the statement of Raiziss and Gavron that the ortho position of the amino radical is essential that in this position, nitro and methyl groups depress the therapeutic activity of the drug: that iodine introduced *into the arsphenamine base removes the trypanocidal effect while it greatly increases the spirillicidal action.* The approach to exact predictability is suggested by the fact that the introduction of two or more amino groups into the arsphenamine base increases the toxicity 20 per cent, while the therapeutic dose remains the same. A substitution in the amino group of the arsphenamine base reduces the toxicity 40 per cent, as in neoarsphenamine, but the minimum therapeutic dose is increased from 23 mg. per kilo in arsphenamine to 40 mg. per kilo in the case of neoarsphenamine, or 10 per cent. It is on the gradual working out of laws such as these governing the behavior of the various radicles involved, as Raiziss and Gavron remarked, that the further advance of chemotherapeutics depends.

Clinical Introduction of "606."—The preliminary tests of "606" on man were made under the direction of Alt, two of whose assistants, Hoppe and Wittneben, volunteered for the first doses intramuscularly N ill effects ensuing, it was used in the treatment of several syphilitic imbeciles, and then, for the first time, in the clinic. The drug, Salvarsan (606) was announced by Ehrlich and Hata before the Medical Association of Magdeburg on March 5, 1910. On December 14 1910, after thousands of doses sent to clinicians *gratis* throughout the world had proved the worth of the drug, it was placed on the market. Stokes recalls the whispered accounts of the amounts of morphine required by the two physicians receiving the first intramuscular doses at Ann Arbor The impossibility of the intramuscular procedure from the practical standpoint, with its pain, sloughs and prolonged encapsulation, led to Ehrlich reluctant acceptance of intravenous administration as developed by Schreiber and by Hoppe and Iverson, for which he predicted reduced therapeutic effectiveness. It is indeed far cry from the suit-case full of burets, tubing and reagents and the surgical ceremonial of the first intravenous injection, t the "hit-run, syringe-and-ampule, shot giving technic of the war days and after

The deluge of press publicity the captivation of medical thought by phrase, the fading of the Ehrlich dream of sterilization by single dose (*therapia sterilisans magna*) under the reports of relapse notably those of Finger on neurorecurrence are really only minor incidents in triumph of constructive thinking that within one decade raised empirical medicine and rule-of-thumb syphilology if only in as yet incompletely fulfilled promise, to the dignity of an exact science.

The Modern Arsenicals.—The subsequent development of other arsphenamines and the revival of arsenoxide has been beset with many difficulties Neoarsphenamine the sulphoxylate compound and the 914th member of the series has demonstrated if nothing else, the vast importance of technical simplification and elimination of inconvenience and discomfort for the patient, in the practical adoption of an idea by the medical profession. The First World War was literally won syphilologically speaking, on the syringe technic for neoarsphenamine devised by Ravaut. The second will perhaps be won on the simplifications of arsenoxide. A superior drug, arsphenamine proper or 606 is passing into the discard because it is difficult for the average doctor to give The distinctive contributions of later years have been silver arsphenamine (Karrer Kolle) sulpharsphenamine (Voegtlin) identical with myosalvarsan (Kolle) bismuth arsphenamine sulphonate (Raiziss) the two latter intended for intramuscular use, both for technical reasons and in the effort to restore the Ehrlich tradition of intramuscular superiority In the past decade beginning with the work of Tatum and Cooper (1932 1934) and continued by numerous other investigators favorable results have been reported from the clinical use of the hemialcoholate of 3-amino-4 hydroxyphenylarsine oxide

hydrochloride (mapharsen) This preparation and 3-amino-4-hydroxyphenyl dichloro-arsine hydrochloride (dichlorophenarsine hydrochloride, phenarsine hydrochloride, clorarsen) used in the long standard systems or in foreshortened treatment are now dominating the investigative field

It required the disrupting forces of the First W to release the study and fabrication of the arsphenamine group of drugs from the German control of patents, with the initiation of American manufacture by Schamberg Kolmer and Raiziss. Forthwith, each nation adopted a terminology of its own for its own products, including Kharsivan, arsenobenzene diarsenol, and so forth salvarsan remains the German designation for the group, and arsphenamine (ars-phen-a-meen) the official and now widely used American term. Arsenobenzol is probably the generic international term.

Toxicity Controls and Choice of Product.—The toxicity controls for different nations vary but the underlying principles have been described. In the United States they are in the hands of the National Institute of Health of the United States Public Health Service. International conferences have resulted in greater uniformity of practice (League of Nations Health Organization, 1925 1928) Regulation could be materially extended by utilizing known facts on perishability and variability of lots through a system of dating plus an effort at therapeutic standardization based on spirillicidal rather than trypanocidal action. The difficulties, however are considerable If an arsphenamine "misbehaves," the physician, after a rigorous inquiry into his own technic, should send duplicate samples of two ampules each from the offending lot (see control number on ampule) to the manufacturer and to the National Institute of Health, United States Public Health Service, Bethesda Station, Washington D C., with a full statement. Government control at first withheld has now been extended to mapharsen. The pentavalent arsenicals (tryparsamide) are not controlled.

The question frequently asked by the practicing physician as to which arsphenamine is best among a number of manufacturers products can be honestly answered at the present day in this country by the statement that all arsenicals subjected to Government control and of a well-known standardized type are, like all automobiles of responsible manufacture, good.

Miscellaneous Nonspirillicidal Arsenicals.—A deluge of preparations capitalizing the concept of "arsenic as an antisyphilitic agent without regard to chemical constitution or serious investigation of claims, has flooded the market since "606. It must not be imagined that because drug is an organic arsenic synthetic or because it merely contains arsenic, that it has any value whatever in the treatment of syphilis. Arsenical tonic effects re good enough in their place, and obtainable with variety of preparations such as the cacodylate, arsenious acid, and so forth, but they have no place hatever in the treatment of syphilis by the use of spirillicides. "Monarson, "Venarsen, and similar preparations have nothing in common except the syllable ars with the modern arsphenamine therapy of syphilis. The practicing physician should therefore select his arsenical armamentarium with reference to syphilis on the basis of careful study of authoritative orks and the practice of well-organized schools and clinics, rather than from the advertising pages of journals in these days of pharmaceutical enterprise.

The Arsphenamine Discard.—It is inevitable that experimental chemotherapy will give birth to preparations of only ephemeral value or inevitably and naturally replaced by others of superior merit. The slow process of evaluation will inevitably compel many frank revaluations and many reversals of opinion. Among the drugs hich have reached or are approaching eclipse may be mentioned silvarsan sodium, or neutral arsphenamine, the sodium salt of the arsphenamine base neosilverarsphenamine, rated by Raiziss as one-half as toxic as silver arsphenamine and slightly more toxic than neoarsphenamine galyl" (Mouneyrat 1116), phosphoarsphenamine of French origin very popular during the first orld war but with no demonstrated advantages and supposed sodium salt of this drug hich is in reality nothing more than an illustration of the chemical legerdemain which lies between the paper constitution of synthetic arsenical

concluded as his experience increased that to secure maximum spirillicidal efficiency the reduction must be performed for the body not by it.

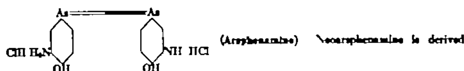
Next, utilizing an observation from his experience with azo dyes, Ehrlich grasped the importance of the ortho position of hydroxyl and amino groups in producing trypanocidal drugs. The aminophenylarsenic acids followed and then by another reduction with sodium hydrosulphite, the arsphenamin base and its dihydrochloride, the 606th of series of compounds elaborated by Ehrlich and his coworkers. The halogen plays an essential rôle even in this drug, so generally thought and spoken of by the physicians who use it and its derivatives, as "arsenic.

The intricacy of the intramolecular chemistry of these dyes is illustrated by the statement of Raiziss and Gavron that the ortho position of the amino radical is essential that in this position, nitro and methyl groups depress the therapeutic activity of the drug that iodine introduced *into the arsphenamine base removes the trypanocidal effect while it greatly increases the spirillicidal action.* The pproach to exact predictability is suggested by the fact that the introduction of two or more amino groups into the arsphenamine base increases the toxicity 30 per cent, while the therapeutic dose remains the same. A substitution in the amino group of the arsphenamine base reduces the toxicity 40 per cent, as in neoarsphenamine, but the minimum therapeutic dose is increased from 25 mg. per kilo in arsphenamine to 40 mg. per kilo in the case of neoarsphenamine, or 16 per cent. It is on the gradual working out of laws such as these governing the behavior of the various radicles involved, as Raiziss and Gavron remarked, that the further advance of chemotherapeutics depends.

Clinical Introduction of "606."—The preliminary tests of "606" on man were made under the direction of Alt, two of whose assistants, Hoppe and Wiltneben, volunteered for the first doses intramuscularly N ill effects ensuing, it was used in the treatment of several syphilitic imbeciles, and then, for the first time, in the clinic. The drug, Salvarsan (606) was announced by *Ehrlich and Hata before the Medical Association of Magdeburg on March 3, 1910. On December* 14 1910, after thousands of doses sent to clinicians *gratis* throughout the world had proved the worth of the drug, it was placed on the market. Stokes recalls the whispered accounts of the amounts of morphine required by the two physicians receiving the first intramuscular doses at Ann Arbor The impossibility of the intramuscular procedure from the practical standpoint, with its pain, sloughs and prolonged encapsulation, led to Ehrlich reluctant acceptance of intravenous administration as developed by Schreiber and by Hoppe and Iverson, for which he predicted reduced therapeutic effectiveness. It is indeed far cry from the suit-case full of burets, tubing and reagents and the surgical ceremonial of the first intravenous injection, to the "hit-run, syringe-and-ampule, shot giving technic of the war days and after

The deluge of press publicity the captivation of medical thought by phrase, the fading of the Ehrlich dream of sterilization by angle dose (*therapia sterilisans magna*) under the reports of relapse, notably those of Finger on neurorecurrence are really only minor incidents in triumph of constructive thinking that within one decade raised empirical medicine and rule-of-thumb syphilology if only in as yet incompletely fulfilled promise, to the dignity of an exact science.

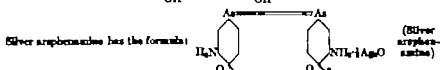
The Modern Arsenicals.—The subsequent development of other arsphenamines and the revival of arsenoxide has been beset with many difficulties Neoarsphenamine the sulphoxylate compound and the 914th member of the series has demonstrated if nothing else the vast importance of technical simplification and elimination of inconvenience and discomfort for the patient, in the practical adoption of an idea by the medical profession. The First World War was literally won syphilologically speaking, on the syringe technic for neoarsphenamine devised by Ravaut. The second will perhaps be won on the simplifications of arsenoxide. A superior drug arsphenamine proper or "606" is passing into the discard because it is difficult for the average doctor to give The distinctive contributions of later years have been silver arsphenamine (Karrer Kolle) sulpharsphenamine (Voegtlin) identical with myosalvarsan (Kolle) bismuth arsphenamine sulphonate (Raiziss) the two latter intended for intramuscular use both for technical reasons and in the effort to restore the Ehrlich tradition of intramuscular superiority In the past decade, beginning with the work of Tatum and Cooper (1932, 1934) and continued by numerous other investigators, favorable results have been reported from the clinical use of the hemialcoholate of 3-amino-4 hydroxyphenylarsine oxide



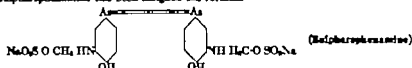
Neoarsphenamine is derived from the arsphenamine base by the substitution of sodium monomethylene sulphonat group attached to one and also to part of the second amino radical. Its formula (approximate) is as follows (after Voegtlin)



Silver arsphenamine has the formula:

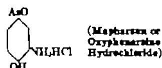


and sulpharsphenamine has been assigned the formula

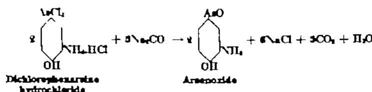


Bismuth arsphenamine sulphonate is a compound of sulpharsphenamine and bismuth.

Mapharsen is the trivalent arsenical which is the hydrochloride of meta-amino-para-hydroxy-phenylarsine oxide. It is obtained from alcohol ether solution in the form of hemi-alcoholat which is a white fluffy hygroscopic powder. It contains 29 per cent arsenic in trivalent form. In the dry state it is stable but in contact with air and moisture it gradually darkens. The name, mapharsen, has been constructed from the chemical term. Structurally it is represented by the formula,



Dichlorophenarsine hydrochloride, 3-amino-4-hydroxyphenyl dichloro-arsine hydrochloride (dichlorophenarsine hydrochloride, clorarsen, phenarsine hydrochloride), is a trivalent arsenical preparation containing 26 per cent arsenic which is available on the market with sufficient alkaline buffering agent (sodium citrate or sodium carbonate) to make neutral prepared solution for injection. On the addition of sterile distilled water to an ampule containing the mixture of dry dichlorophenarsine hydrochloride and alkaline buffer a reaction takes place with the result that arsenoxide is formed. This reaction is represented as follows:



Preparation of Arsenicals for Administration.—All the arsphenamines are yellow powders with the exception of silver arsphenamine, which is brown and yields a brown solution. The aqueous solution of "606" is strongly acid and

the solubility of the drug is less than that of any of the other derivatives, formerly requiring hot water to put it into solution. The acid solution of arsphenamine "606" cannot be injected intravenously in any considerable concentration without the most disastrous results. In order to prepare the solution for administration it must be neutralized by the addition of normal sodium hydroxide which first of all precipitates the insoluble base as a yellowish white precipitate. As a further addition of the alkali takes place this yellowish white precipitate of the arsphenamine base redissolves as a monosodium salt. This in turn, on still further addition of the alkali, is converted into the still soluble disodium salt of the arsphenamine base, yielding a canary yellow solution with a pH of from 9 to 10 Only in this form and in the proper dilution can the drug be safely injected into the blood, though the monosodium salt or a mixture of mono- and disodium salts can be injected under proper precautions by those experienced in its use.

The arsphenamine disodium salt solutions are hemolytic in all concentrations. One of the chief sources of acut nitritoid reaction t the drug has been show by the excellent work of Oliver and his collaborators to be the tendency of the disodium salt to agglutinate red blood cells This can be overcome to some extent by buffering the solutions with gelatin, method that has not, however gained foothold in practice In our personal experience the original technic of preparing arsphenamine solutions under proper precautions with 0.6 per cent physiologic saline has distinct advantages on the score of reduced reactivity and better tolerance by the veins. The question as to the relative safety and merit of mixtures of monosodium and disodium salts as compared with the disodium salt alone is debatable.

Neoarsphenamine and the other widely used derivatives escape the serious and sometimes tragic defect of requiring neutralization for their safe administration. This neutral reaction in solution by simplifying the administration technic with a lower tendency to immediate reaction, undoubtedly accounts for their vastly greater popularity in practice. Neoarsphenamine as a powder and in solution is a distinctly darker yellow than "606" and manufacturers have prided themselves on the development of what is called flash-solubility" or almost instantaneous solution of the drug in water at room temperature. This characteristic, which sharply differentiates neoarsphenamine in the process of preparation in the treatment room from the much slower-dissolving arsphenamine while useful, is rather overstressed in salesmanship It is none the less true that neoarsphenamine that will not immediately go into solution in 10 cc. of water at room temperature may present serious defects and should be discarded. Sulpharsphenamine is dissolved in 2 cc. of water silver arsphenamine and mapharsen, like neoarsphenamine in 10 cc. of water and bismuth arsphenamine sulphonate in 1 cc of water for the accustomed therapeutic dose

The arsenical content of the arsphenamines is very variable but is pproximately as follow Arsphenamine (606) 30 per cent neoarsphenamine (914) 19 per cent, sulpharsphenamine 19 to 20 per cent silver arsphenamine 12 to 14 per cent silver and 19 t 20 per cent arsenic; mapharsen 29 per cent; bismuth arsphenamine sulphonate, 21 per cent bismuth, 13 per cent arsenic. While it is easily possible from these figures t obtain the arsenical content in milligrams of each dose of an arsphenamine that is given, it should be fully realized that no such method of estimating the therapeutic dosage of arsphenamine compounds is satisfactory because the therapeutic effect is, as has already been emphasized, dependent upon many other considerations besides the arsenic content. Thus, as ill presently be pointed out, the arsenical content of tryparsamide is approximately equal t that of "606" but its spirochetocidal properties are negligible notwithstanding its effectiveness in penetration of the nervous sy tem and treatment of paretic neurosyphilis. Within given group, however Voegtlin et al. have show that the sterilizing power of massive dose of arsphenamine neoarsphenamine or sulpharsphenamine in the rabbit i precisely equiva-

lent to the arsenical content, which is the same in all three instances, regardless of the difference in the dose of the compound administered and regardless of whether it is given in one dose or divided among series (Voegtlin, *et al.*)

Preparation of Arsenoxid (Mapharsen) for Administration.—Mapharsen in the ampule should be a whit crystalline powder and if color changes have occurred, it should be discarded It goes into solution readily in 10 cc. of water and in contrast to neoarsphenamine, aeration by the bubbling of the solution and the squirting of the solution back and forth by the syringe is method of releasing toxicity For clinical use mapharsen, according to the manufacturer's directions, is supplied mixed with sufficient amount of alkali and sucrose to make the aqueous solution practically neutral and isotonic with the blood Again in contrast t neoarsphenamine, the mapharsen solution should be administered rapidly instead of slowly; again from the directions, "the time elapsing from the insertion of the needle until the syringe has been emptied and the needle removed from the vein should be no more than thirty seconds.

The Biological Chemistry of the Arsenicals.—The arsphenamines, whether injected intravenously or intramuscularly are taken up by the blood stream and are carried to all the tissues of the body The distribution of arsenical drugs to tissues differs in the case of organic as compared with inorganic compounds. Underhill and Dimick, working with dogs showed that the quantity present in the tissues did not necessarily depend on the amount given or on the number of injections. A sharp line is thus to be drawn between administration and penetration and still another line can be drawn as Osborne and his co-workers have suggested between penetration and metabolizing of an arsenical drug

Work on the presence and distribution of arsenic in the circulation of the body tissues has been serious field of controversy now it is to be hoped, about to be resolved by the use of radioactive arsenic as foreshadowed by the recent studies of duPont and her associates (1942) of the distribution of the tagged atom in the normal and tumor-bearing rabbit. Riebes early showed that arsphenamine as such is present in the blood about three hours, but might persist for longer periods in patients who react. Fordyce, Rosen and Myers found marked difference between patients in their disposal of injected arsphenamine, permitting definite classification of patients into two groups—those who retain and those who rapidly eliminate arsenic. On the average, they found 60 per cent of the arsenic administered in an intravenous injection of neoarsphenamine to be localized outside the blood-stream by the time the injection is completed. The controversy regarding differences in localization of trivalen and pentavalent arsenicals with particular reference to the blood-vessel walls, has involved the work of Osborne, using microchemical method of Justus and observers like Tannenholz and Muir (1933) and Oppenheim and Fantl (1934) who were unable to confirm Osborne findings. There are many reasons, both clinical and chemical for suspecting that the arsphenamines are vasculotoxic, an extremely important fact in their reaction-producing characteristics and their therapeutic effect. Chaney and Magnusson (1940) have proposed colorimetric microchemical method for determination of arsenic which may overcome some of the inherent difficulties. Osborne has proposed that the pentavalent arsenicals are to be regarded as neurotropic and the trivalent as vasculotropic.

Notwithstanding the inherent difficulties of chemical analyses for arsenic, fair and indeed, the best available picture by the older procedures, of the distribution of arsenic in the body following the injection of arsphenamine, is given in Figure 86. Following the administration of the arsphenamines, arsenic also appears in the perspiration (Ullmann), saliva (Obregia and Carnol) vomitus, probably due to regurgitation of bile from the duodenum (Weiss and Raiziss), and the milk of lactating women. With the trivalent arsenicals, the nervous system contains only very minute amounts of arsenic, for which Schamberg proposed the view that the easy penetration of serous membrane by crystalline pentavalent arsenicals permitted concentration of arsenic in the nervous system of these drugs, and corresponding failure to penetrat on the part of the colloidal trivalent arsenical preparations.

Arsenical Penetration under Fever and in Pregnancy—Paulian and Tanasescu (1936, 1937) found that the concentration of neoarsphenamine in the cerebrospinal fluid was greater when the drug as given simultaneously with malaria. This has been denied by Hällstrung and Nordmeyer who concluded that salvarsan as such does not pass into the cerebrospinal fluid, even under favorable conditions as afforded by artificial fever therapy It is probable that salvarsan, being colloid, does not pass the blood-cerebrospinal fluid barrier but passes through the blood-brain

barrier where it exerts its beneficial effect on the diseased nerve tissue. Recent studies show that placental transmission of the arsenicals varies with the stage of pregnancy, the rate of transmission increasing as pregnancy progresses (Eastman and Dippel, 1933, Snyder and Speert, 1938).

Storage of the Arsphenamines.—In the practical use of the arsphenamines it must then be constantly borne in mind that while their accumulation at the site of injection is nil in the case of the intravenous route, and comparatively small or absent in the case of the better absorbed arsphenamines such as neoarsphenamine and sulpharsphenamine, a very real and sometimes serious degree of storage may occur in the liver and spleen, and in the walls of the intestinal tract. Underhill and Dimick found the largest amount of arsenic present in the kidneys, following neoarsphenamine in the dog, but the time after injection and similar factors undoubtedly influence this finding because of the function of the kidney as an eliminative mechanism. There is very little doubt that the distribution of the drug is modified by circumstances not as yet understood and that, as Fordyce wrote and Myers has suggested, individuals may be grouped into

Fig. 86.

ARSENIC CONTENT OF TISSUES, ETC., FOLLOWING ARSPHENAMIN INJECTION

Tissue analyzed.	Normal Arsenic Content.	Voegtlin et al. micromilligrams after 100 min.	Clausen and Jeans milligrams As_2O_3 per 100 gms. after twenty four hours.
Heart	0.50	2.83	0.0025
Spinal fluid	0.69	7.21	
Brain	0.08	1.16	0.0
Skeletal muscle	0.03	0.38	0.0
Lungs	1.91	3.93	0.275
Blood	0.29	5.23	
Spleen	5.53	16.83	0.67
Kidney	0.42	2.58	0.154
Urine	2.66	19.62	0.341
Liver	0.55	16.17	0.830
Bile	1.12	196.54	
Stomach			0.151
Stomach wall	0.36	1.03	
Stomach content	0.11	12.36	
Intestinal tract and content	0.07	6.96	
Duodenum and part of jejunum			0.370
Lower ileum			0.306
Rectum and colon			0.380
Skin	0.20	1.60	
Adrenals			0.0
Bone-marrow			0.0
Embryo		0.22	

two or more types with respect to elimination and so also perhaps in regard to storage. Osborne and coworkers have shown that arsenic is not stored in the adrenals of the rabbit, the damage done by the drug probably being due to vascular injury.

Elimination of the Arsphenamines.—As in the case of the heavy metals, the therapeutic efficiency of an arsenical in the treatment of syphilis is to no small extent a function of its rate of elimination. Within the limits of toxicity there occurs an optimum curve of elimination. If elimination is greatly delayed, toxic effects develop. If it is too rapid, therapeutic effect may conceivably be lessened. Wide individual variations exist here as in storage and metabolism, a fact sufficiently apparent from the conflicting reports of investigators. In the elimination of the drug by way of the urine and feces, which constitute the two important routes, the amounts present are independent of the amount of either excrement but apparently depend on the concentration of arsenic in the blood. A series of injections, according to Underhill and Davis, stepped up the rate of elimination of the drug, which explains the clinical fact that patients given large doses at short intervals may tolerate a longer series than patients receiving smaller doses at longer inter-

vals. The maximum excretion is said to occur on the first and second days after the administration and not on the day the injection is given. Small amounts of arsenic are gradually eliminated over a period of many weeks, the total of this retained arsenic aggregating sometimes 50 per cent of the whole dose (Clausen and Jeans) The partition of the eliminated drug between stools and urine varies with the type of drug given and the number of injections, Underhill and Davis stating that after a series of injections the rate of elimination in the stools is more rapid than in the urine although the arsenic appears later in the stools than in the urine at the start. Clausen and Jeans placed the rate of elimination by the stool as five times as rapid as that by the urine. This is in accordance with Voegtlin's finding of a relatively large proportion of the injected drug in the bile Underhill and Davis believe that they find evidence of a saturation point of the tissues for arsenic comparable to that for heavy metals and suggest the propriety of large initial and smaller later dosage in the majority of cases.

Importance of the Liver.—According to the studies of Kraft and his coworkers (1938) the organ predominantly concerned in the immediate removal of arsenic from the blood stream and its excretion is the liver The intestines and kidneys follow in order The total arsenic in these organs decreases steadily and after two days the intestinal mucosae contain as much as the liver The concentration of arsenic was highest in the spleen during the first hour This organ is the only one which showed a tendency to "fix" arsenic. The other organs usually showed a decrease in concentration. The kidneys generally showed a higher concentration than the liver These studies indicated that, while it does not occur greater quantities of arsenic can be excreted in the urine than in the feces.

Applying considerations with reference to elimination to the conditions of clinical practice one finds in them a justification of the empirical practice of giving a cathartic the day after an arsphenamine administration Differences between the arsphenamines on the score of renal irritation-producing effect, while seldom of great importance clinically will probably tend to follow the rule that neoarsphenamine is more irritating to the kidney than arsphenamine The nonirritating effect of the arsphenamines on the kidney as compared with heavy metals is both clinically and experimentally demonstrated A field of clinical study with important possibilities would seem to be that of the application of test procedures to the presence of arsphenamine in the blood and urine for the purpose of detecting abnormal retention, and hence of storage by the liver and other tissues. For this purpose the Abelin test is sometimes used. (See M C S., Ed II, p. 296) See also duPont, *et al.* (1942) p 237

Mode of Action of the Arsphenamines.—Although the as yet unconfirmed work of Eagle and his associates (1938–1939) (*vide supra*) suggests a direct spirillicidal action for the arsenicals, there are a number of reasons for believing that the arsphenamines do not react directly and solely with the micro-organisms of syphilis, but that the effect is produced by their decomposition products. Foremost among the facts weakening the theory of direct action are the numerous observations beginning with those of Hata on the failure of arsphenamine solutions in concentrations as high as 1 to 1000 to affect either the motility or growth powers of *Spirochaeta pallida* and the demonstration of the "lag" in action of the arsphenamines after their introduction into the body For a period varying from five to eight hours no effect upon the *Spirochaeta pallida* is observable following an arsphenamine injection. Then, coincidently with the appearance of reactive symptoms in the patient, the organisms gradually disappear during the course of the next twelve to twenty-four hours.

The coincidence of reaction which reaches its peak at the 8th hour with the appearance of spirillicidal effect is very striking and strongly suggests that within the latent period one of two things has occurred either the bodily defence mechanisms has been stimulated with extraordinary

rapidity to produce antispirochetal substances of a wholly unknown organic nature, a colossal and almost universal phagocytosis by the reticulo-endothelial system is taking place; or the injected and now stored arsphenamine is being broken down into products having a more direct spirillicidal action than the injected drug itself. The decline in activity and viability of the *Spirochaeta pallida* during the succeeding hours after the fifth certainly suggests that all the work of destruction is not done by fixed cells but is carried on in part by a circulating destructive agent. The search, accordingly, should be for a product of the disintegration of arsphenamine having a high toxicity for the micro-organisms and capable, as in the case of the heavy metals, of being discharged into the circulation from storage depots in the body over a long period of time. A number of the requirements for this theoretical agent are fulfilled by the substance arsenoxide which is an oxidation product of the arsphenamine base. Arsenoxide is extremely poisonous in very high dilutions for trypanosomes in concentrations as high as one to a million.

In spite of the narrow margin of therapeutic and toxic effects of arsenoxide on the host predicated by the experience of Ehrlich and Voegtlin and confirmed by Raiziss and Severac (1935) the direct administration of arsenoxide following Tatum and Cooper by the Foersters, McIntosh, Wieder and Cooper has shown that meta-amino parahydroxyphenyl arsine oxide is a powerful, quick-acting spirillicide. The question as to whether its action is sufficiently sustained to control relapse and its toxicity especially for the liver still require further clinical investigation. Kolmer, Schamberg and Brown have shown that the oxidation of the arsphenamines on standing, yielding arsenoxide, greatly increases their spirillicidal effect.

It has been proposed that the action of the arsphenamines takes place through an arseno-protein combination and Levaditi in his studies of atoxyl proposed for this arsenical the formation of an intermediate compound, trypanotoxyl, the predecessor of his subsequent bismoxyl, as the active toxicological combination. There is no doubt that a certain amount of fixation of arsphenamines in blood corpuscles and serum takes place, and Ehrlich early showed that trypanosomes are likewise capable of fixing the arsphenamines with a loss of pathogenicity in the organisms. This, however, is believed by Voegtlin to be a less credible explanation than that of the direct interaction of the arsenoxide radicle with the sulphhydryl oxidation mechanism of the parasitic cell by way of oxidation-reduction catalysts such as glutathione.

Since Voegtlin, Dyer and Leonard (1923) advanced the hypothesis that sulfhydryl groups present in the protoplasm of the parasite take part in the reaction with the drug and hence should be considered as the "chemoreceptor" there seems to have been little attempt to prove this theory. In 1932 Rosenthal and Leonard, however, advanced further experimental evidence corroborating the previous findings concerning the antagonistic effect of thiol (sodium thioglycollate) compounds on the physiologic activity of organic arsenious oxides. Eagle (1939) contributed additional support to Voegtlin's thesis by showing that sulfhydryl compounds (cysteine, glutathione, and thioglycollic acid) added in sufficient excess to arsphenamine, neoarsphenamine, silver arsphenamine, arsenoxide, bismuth or mercury compounds almost completely abolish their antispirochetal activity in vitro. The large excess which is necessary suggests that the addition compound may be hydrolyzed. Thiamine chloride and methionine which contain a —S— rather than a —SH group have no inhibitory effect. Eagle recognizes the possibility that the spirocheticidal activity of the arsenicals, bismuth and mercury compounds may be due to a chemical reaction which bears no relationship to their affinity for and inactivation by sulfhydryl compounds.

It will be apparent from this highly condensed survey that the original Ehrlich receptor theories of the direct linkage of the arsphenamines with the parasites they attack have given way to more complex conceptions none of which may be said as yet to have received unqualified endorsement. In all probability, as in the case of the action of nonspecific protein and fever therapy, multiple modes of action are involved in which each proponent may claim a share for his particular conception. Tatum (personal communication to Moore 1942) and Simpson (1942) approaching from widely different angles, have well stated the problem in saying that it is not the quantitative arsenical content or location, but what the arsenic does when it reaches the spot which is important in its chemotherapeutic effect. Before the problem is worked out, not only the metabolism of chemotherapeutic compounds by the body but the metabolism of protozoa and spiral organisms must receive far more extended study.

THE PHARMACOLOGY AND TOXICOLOGY OF THE ARSPHENAMINES

When it is considered that the maximum adult dose of "600" and its congeners in therapeutic equivalents introduce into the body and usually directly into the blood stream something approximating twenty-six times the fatal dose of arsenic, the range in variety of toxicological manifestations produced by this group of drugs is quite to be expected and the wonder grows that with the thousands of doses given each day and the millions each year throughout the world the toll of grave damage and fatal outcome is not appalling instead of relatively trivial. While however the triviality is apparent in the aggregate, it disappears at once in the concrete and a physician, watching with perplexity and alarm the outcome of his "shot has good need of detailed knowledge as well as rule-of thumb in comprehending and dealing with an arsphenamine on the rampage

In order to make apparent the fundamental resemblances between the heavy metals especially bismuth and the arsphenamines, as well as to catalog for convenient reference the range of arsphenamine toxicological manifestations, we have prepared Fig. 87 which may well be compared with Fig 75 page 201 for bismuth. It will at once be apparent that while there is a general resemblance based on absorption and elimination phenomena, the greater solubility of arsphenamine compounds and the possibility of their direct introduction into the blood stream leads to a much larger proportion of vascular injury perhaps than occurs with the bismuth compounds, although vascular injury of a more chronic type is again important with mercury Like bismuth, the arsphenamines spare the kidney but to an even greater degree. The toxicity of an arsphenamine for the kidney has been rated by Schamberg, Kolmer and Raiziss as only one fiftieth that of mercury The disposition of the trivalent arsenicals to injure the vascular system affects every aspect of their reaction producing quality and must constantly be borne in mind in their therapeutic use, while the effect of these drugs on the kidney could were they used exclusively be almost forgotten

McFarland showed very clearly in his study of the behavior of the kidney under treatment for syphilis that in the mercurial days it as mercury which introduced all the renal complications into treatment with the single exception of the fulminating anuria that may follow the administration of an improperly neutralized "606"; and the same principle has been borne out in the American Cooperative Clinical Group study of complications under treatment for early syphilis. In this latter series of studies not only did the heavy metals as source of renal reactivity appear as of major importance, but the arsphenamines when used alone or with little heavy metal proved throughout the entire range of reactivity to be by far the most innocuous part of modern treatment for syphilis. This finding lends decided color to the generalization so frequently insisted upon by Schamberg, for example, that the toxicity of the heavy metals for the eliminative mechanism and particularly of mercury for the kidney gives rise to phenomena of arsenical intoxication through abnormal retention of the drug by an overloaded or injured eliminative mechanism. On the other hand, the resemblances between the types of reaction produced by arsphenamine and the heavy metals suggest that part of the increased reactivity under combined treatment may result, so to speak, from striking the same spot with two fists.

New Reaction Classification.—In our more recent discussion of arsenical reactions, we have tended to use a new type of classification, emphasizing the induction and incrimination of allergic factors in the arsenical-reactive picture, but especially conspicuous in the arsphenamines.

1 *Idiosyncratic Allergic Phenomena* —Hemorrhagic encephalopathy aplastic anemia most cases of exfoliative dermatitis.

TOXICOLOGY OF THE ARSENICALS IN MAN

I. **Local reactions at injection sites.**
   1 **Pain, induration, necrosis.** Most marked with "606, and arsenoxide (mapharsen) almost negligible with other arsenicals. Gangrene of hand due t neoarsphenamine or arsphenamine (Newman nd Giles; Sutter Oddo nd Giraud Schloffer) (intra-arterial injection? acid solution? arsenical endarteritis obliterans?).
   2. **Vein spasm.** Usually due to hyperalkalinity but rarely idiosyncratic and accompanied by local hemorrhagic injury
   3. **Venous thrombophlebitis.** Common with mapharsen if injected slowly
   4 **Abscess.** Rare

II. **Systemic Reactions.**
   1 **Vascular**
      ( ) **Nitritoid or vasomotor crisis** (especially after intravenous, but also intramuscular use) Due t agglutination of red blood cells (capillary emboli) (Oliver Douglas *et al.*) liver cell injury from rapid injection (Hirshfeld, Hyman nd Wanger) and other undefined causes. Rare after arsenoxide (marpharsen)
      (*b*) **'Colloidoclastic shock.** Collapse and death immediat or preceded by coma or convulsions, jaundice and nuria. Most often due to acid 606 (unneutralized) but may rarely be idiosyncratic
      (*c*) **Capillary and finer blood vessel injuries as in:**
         Hemorrhagic encephalopathy (edema and punctat hemorrhages of brain)
         Purpura haemorrhagica.
         Hypotension, collapse (possibly adrenal vascular injury—Osborne)
         Raynaud syndrome.
         Cutaneous injury (vascular factor in cutaneous eruptions, especially toxic erythema, urticaria, dermatitis (Osborne)
      (*d*) **Fatal medical shock** (Orr; Weinberg) shock-like reactions t the arsenicals, adrenal injury (?)
      ( ) **Acute interstitial myocarditis** (Brow and McNamara) associated with arsenical dermatitis (allergic.)
   2. **Stomatitis:** Rare, occasionally accompanying dermatitis and aplastic anemia. N pigment, fetor et
   3. **Gastro-intestinal tract** Vomiting, diarrhea rarely ulcerative colitis (ith dermatitis) Gastric ulcer perforation.
   4 **Nervous system** Rare peripheral neuritis (foot and wrist drop) polyneuritis. Optic nerve injury theoretical but unestablished. Arsenical myelitis. Encephalopathy Arsenical herpes. Nervous tension and insomnia.
   5 **Skin** Cutaneous allergy induced pruritus, urticaria; erythema multiforme macular papular morbilliform, scarlatiniform, pemphigoid fixed exanthem, arsenical (or silver) pigment and keratoses (rare); herpes (rare) lichenoid and follicular papular eruptions (pseudo-lichen planus); pityriasis rosea-like eczematoid patchy eruptions, dermatophytic flare-ups flare-ups of seborrhoeic dermatitis arsenical exfoliative dermatitis.
   6. **Liver** (rather rare) Acute arsphenamine jaundice (arsenical hepatitis) lat arsphenamine jaundice acut yellow trophy chronic arsenical hepatitis (Warthin) intercurrent infectious jaundice on predisposed arsenical-injury background.
   7 **Kidney** (rare) Treatment nephrosis anuria, usually after acid 606.
   8. **Adrenals** Direct or vascular with Addisonian symptoms, hypotension collapse A rare nd even doubtful reaction.
   9 **Respiratory system** Bronchitis (ith dermatitis) Bronchopneumonia after 606. Pulmonary embolism and subsequent bronchopneumonia from arsenicals, other than 606, if pH of solution is less than 7 (Shivers) Asthma (Klauder Saunders, 1932)
   10. **Joints** Arthritic reaction ith erythema multiforme
   11 **Blood** Hemolysis, agglutination (606, 914) agranulocytosis plastic anemia ith stomatitis and purpura (sulphoxylat arsphenamines, especially sulpharsphenamine)
   12. **Allergic reactions** Cutaneous, pulmonary vascular (nitritoid) as above included under various heads.
   13. **Therapeutic shock effects:** Not properly classifiable as arsphenamine reactions.

NOTE HOW MUCH ARSENIC AND BISMUTH HAVE IN COMMON

2. *Infection Allergic Phenomena*.—Milian ninth day erythema, some exfoliative dermatitis, urticaria, the intercurrent infection factor apparent in jaundice, and in the periodicity or wavelike character of other types of reaction.

3. *True Drug Reaction Phenomena*.—Arsenical hepatic atrophy, polyneuritis, true arsenical dermatitis, eczema and pigmentation, pigmentary and fixed eruption.

4. *Technical Reaction Phenomena*.—Nitritoid crisis, speed and colloidoclastic shock, gastro-intestinal reaction.

This classification lacks consistency in some points, in that nitritoid crisis, for example, contains allergic elements, and gastro-intestinal reaction may be true drug reaction rather than a technical matter. The classification, however, has suggestive value in the interpretation of interrelations between focal and intercurrent infection and reaction incidence and precipitation, and in explaining some of the sequences and characteristics of the more fatal reaction phenomena which appear to involve special structures like the capillary vascular system of the brain, the bone marrow, and so forth.

Arsphenamine Local Reactions.—The local reactions produced by the arsenicals are due fundamentally to arsenic and when leakage around an improperly entered vessel occurs in any considerable amount, the characteristic violent inflammatory reaction followed by the extraordinarily persistent arsenical slough may be expected. The alkalinity of solutions of "606" is possibly a contributing factor. In the more recent arsphenamines, however, such as sulpharsphenamine and bismuth arsphenamine sulphonate, local necrotic action has been reduced to the point where the drug is entirely tolerable and in fact rapidly absorbed. Abscesses are almost unknown with the less irritating drugs under aseptic technic. Vein spasm and venous thrombophlebitis are almost entirely confined to "606" and mapharsen. Thrombophlebitis has a distinct element of hypersensitivity though it is more often due to incorrect preparation of the solution with hyperalkalinization. Thrombophlebitic changes are apt to occur in any vessel showing repeated spasm and can be recognized by the cordlike feel under the finger at the next treatment session and history of tenderness or pain during the preceding week.

In the extremely rare cases of idiosyncratic local hemorrhagic injury, the slightest attempt to inject arsphenamine results in almost instantaneous spasm with violent pain, blanching of the surrounding skin and, if injection is persisted in, frequently by suggillation and hemorrhage, especially if the vessel be of small caliber. Thrombophlebitis promptly closes the vein. Newman and Giles (1940) have reviewed the subject of gangrene of the extremities due to arsenical injection. The exact mechanism of this effect is unknown.

Systemic Intoxicating Effects of the Arsphenamines—Vascular Injuries.—The effect of the arsenicals on the heart is discussed under Reactions (Chapter IX) and Cardiovascular Syphilis (Chapter XIX). The group of vascular injuries is one of fascinating interest and the acute vasomotor or vascular crisis spoken of as the nitritoid reaction has probably its best examples and has been most thoroughly studied in the field of arsphenamine therapy. The identical reaction may occasionally occur after bismuth injections and such nonspecific treatment as the intramuscular administration of boiled milk. Nitritoid reactions occur after all of the arsphenamines, most frequently after "606," rarely but none the less definitely after the intramuscular drugs and almost never with mapharsen. The clinical aspects of the reaction are described in detail on page 409.

The Nitritoid Reaction.—This still remains a puzzle notwithstanding the long history of competent investigation, for which, to save space reference is made to the second edition of this text. A variety of considerations point to an anaphylactic or anaphylactoid mechanism tied in with the rate of administration of the drug, and probably associated with the complexity of the molecule and the colloidal character of the solution since such reactions are almost completely absent with mapharsen, notwithstanding its rapid rate of injection. The influence of atropin in protecting against reaction, the possibility of inducing Besredka-like phenomenon of protection by a preliminary small dose, the intravascular agglutination of red blood cells (Oliver Douglas and Yamada) are suggestive of this type of mechanism. There is evidence of a distinct idiosyncratic quality to the reaction in certain patients, of its gradual development in a manner comparable to sensitization by repeated assault, and in the clinical symptomatology which is in some particulars quite comparable to anaphylactic shock. Hirshfeld, Hyman and Wanger in their studies of so-called "speed shock," have related the mechanism to injury inflicted on the liver cell as a function of the rate of introduction of the offending substance. It is also possible that some of the symptoms may be due to the liberation of histamine or histamine-like substances into the blood-stream under the influence of the drug as in Sir Thomas Lewis' explanation of anaphylactic phenomena. We have had occasion to suspect strongly on clinical grounds that the sympathetic nervous system participates in nitritoid types of reaction and shock, and they have seemed more common in individuals with sympathicotonic characteristics and an intense nervous anxiety. While intrinsically of little more than subjective importance as a highly disagreeable episode for the patient, easily developing or frequently recurring nitritoid crisis may be interpreted as a warning of possible serious vascular dysfunction or injury.

Colloidoclastic Shock.—This reaction produced by the arsphenamines is a function of their colloidal behavior in solution presumably and in its most severe form is a fulminating and fatal affair. Colloidoclastic changes, of course, inevitably follow the injection of acid "606," especially in any considerable concentration, and it is this which is responsible every year for fatalities in clinics and practice which should be preventable. If the patient's life is not immediately extinguished by the shock, a period of coma or convulsions preceded by agonizing pain in the kidney region and followed by anuria and perhaps jaundice declares the profound and probably arsenical character of the intoxication. On the other hand, these incidents are at times apparently absolutely idiosyncratic. Fortunately they are very rare. Colloidoclastic shock is apparently identical with "medical shock" following neoarsphenamine, as discussed by Orr (1933) and Weinberg (1937). Adrenalin does not relieve the condition.

Other Types of Capillary Injury—Hemorrhagic Encephalopathy.—The other types of capillary and finer blood vessel injury associated with the arsenicals again have the quality of extreme gravity. Hemorrhagic encephalopathy, also called "brain purpura" and arsphenamine encephalopathy, more fully described under Reactions (p. 434) is an acute edema of the brain with innumerable capillary hemorrhages throughout its substance, and is a chief cause of death from the arsphenamines. Glaser and the Imermans have pointed out that the reaction occurs in nonsyphilitic persons, apparently without relation to age or sex, or to the dosage of the drug administered, the number of injections given, or to the intrinsic toxicity of the preparation. The reaction occurs most commonly after the second dose, may develop within twelve hours or after a latent period as long as several days. The autopsy picture in the brain is that of dilatation and engorgement of meningeal and cerebral vessels with a picture suggesting "wet brain," plus vascular necrosis and perivascular hemorrhage of the "ringed" type. It may occur with or without universal purpuric accompaniments, the patient, after a brief period of mental confusion lapsing into coma punctuated by convulsions and in the large majority of cases terminating in exitus. The resemblance of the edema to that associated with delirium tremens has been pointed out.

The hypotension which frequently follows arsphenamine administration in reacting patients is theoretically related to the adrenal mechanism because of its response to epinephrin and ephedrin. In a patient with the Addisonian syndrome associated with syphilis, one of us (J. H. S.) was able after each

arsphenamine injection to watch the course of the vasomotor collapse and slow recovery after arsphenamine very much more marked than in any patient previously observed and accompanied by a deepening in pigmentation, extreme weakness and diarrhea. This was in the prebismuth days.

Osborne's investigations certainly suggest that a large part of the cutaneous injury produced by the trivalent arsenicals is associated with damage to the capillaries, in whose walls extensive deposits of arsenic can be demonstrated to the exclusion of other skin structures, which are more apt to be affected by the pentavalent arsenicals. Presumably this factor operates likewise in the erythema multiforme groups of vascular injury.

Injuries to the Gastro-intestinal Tract.—Those inflicted by the arsphenamines tend to be acute, soon over and rarely serious. They are least frequent with mapharsen. Stomatitis, so characteristic of the heavy metals, is an extreme rarity under the arsphenamines, being as often though not necessarily an accompaniment of exfoliative dermatitis, in which the inflammatory process seems to involve the mouth together with the gastro-intestinal and respiratory tracts, and aplastic anemia, in which there is probably no direct causal relation except the underlying arsenical intoxication. Pigment, fetor and so forth do not occur in arsphenamine stomatitis and in fact the ability of these drugs to contribute to the sterilization of the mouth with respect to saprophytic and especially Vincent's flora, makes them have actual prophylactic value in dealing with heavy metal stomatitis.

The reactions of the upper gastro-intestinal tract are probably associated with the elimination of the arsphenamines through the bile as they are metabolized in the liver. On the other hand, the lower intestinal tract exhibits, as Osborne has shown, marked deposition of arsenic in the mucosa and muscular layers (there is also some deposition in the walls of the upper intestinal tract) and this, as in the case of bismuth, explains the more serious symptoms, including ulceration of the colon which may accompany profound arsenical intoxications with and without dermatitis. The damage done to the gastro-intestinal tract by arsenic is perhaps contributory to the perforation of gastric ulcers occasionally observed under arsphenamine treatment even though marked vomiting has not occurred.

Injuries to the Nervous System.—The relative rarity of other than vascular lesions of the nervous system among arsphenamine reactions is notable. Peripheral neuritis, heralded by tingling, and much more leisurely in its onset than that characteristic of lead, for example, occasionally occurs under high dosage arsphenamine treatment, especially among the first cases treated by massive arsenotherapy. Polyneuritis is a not uncommon accompaniment of severe intoxication; arsenical myelitis occurs in conjunction with intraspinal therapy rather than otherwise where the drug is brought into direct contact with nervous tissue, and arsenical herpes zoster occurs as in other forms of chronic arsenical poisoning. The arsphenamines give rise to what will be subsequently alluded to as an "overtreatment syndrome" of nervous tension and insomnia comparable to the effects of bismuth therapy on certain individuals. Encephalitis should be regarded as a vascular reaction rather than one involving the nervous parenchyma as such.

Injuries to the Skin.—The cutaneous toxicology of the trivalent arsenicals (including mapharsen) has practically the same range as bismuth but a distinctly greater frequency and graver character. The simplest reaction, pruritus, may occur alone and repeatedly but is usually a warning of something more

serious to come. Together with urticaria and exfoliative dermatitis it may form part of the expression of the true cutaneous allergy which has now been shown both clinically and experimentally to be produced by drugs of the arsphenamine series. This phase of arsphenamine toxicology is considered separately below. The erythema multiforme types of reaction are usually sharper than those observed with bismuth and probably express the vascular injury produced by the drug plus its influence as suggested by Milian in activating or lighting up foci of infection containing streptococci such as are known to be associated with this type of reaction in patients not receiving treatment for syphilis (see Ninth Day Erythema, page 419). The arsphenamine fixed exanthem is an eruption of peculiar interest in that it is of a type known to occur also with drugs of the antipyrin type and likewise with phenolphthalein (Chargin and Leifer 1940). The recurrence of urticarial lesions *in situ* over and over with successive administrations of the drug until the two or three individual areas involved become lichenified and to some extent eczematous is a clinical phenomenon wholly without basic explanation. Atrophic changes may also occur (poikiloderma-like changes Cannon *et al* 1942), reticular fibro-atrophoderma following arsphenamine dermatitis (Epstein 1938). Pigmentation and keratoses are fortunately rare complications. Pigmentation from silver arsphenamine has been reported by Kogoj and recently in the American literature by Spiegel and by Becker and Ritchie *et al*. The distribution of arsenic has been studied by Osborne. Vitiligo has been extensively studied by Cannon and Karelitz (1933). Herpes is a rarity and may be both of the simple and zoster type. The simulation of lichen planus by the lichenoid arsenical eruption is so exact that in view of the developing conceptions of lichen planus (see p 552) as an associate of sympathetic nervous system disorders, it seems not improbable that a similar nervous mechanism may be involved in arsphenamine lichen planus. Peripheral gangrene and Raynaud's syndrome have been reported by Nicolas, Massia and Dupasquier (*vide supra*). The ability of the arsphenamines, probably through their arsenical content, to influence other dermatoses occasionally gives rise to false impressions. For example a pityriasis rosea-like exanthem may occur particularly with bismuth arsphenamine sulphonate as with bismuth; patchy eczematoid eruptions are well recognized as associated with arsenic and sometimes difficult of diagnosis. Flareups of seborrheic, mycotic and occasionally pyogenic processes, have been noted by Lees, Harrison and Smith (1938). Stokes and Kulchar have discussed the infection allergic implications. One of the most interesting and confusing of these pictures is the flare-up of inguinal and peri anal dermatophytosis with the appearance of patches on the body that is not infrequently confused by the inexperienced with a relapsing secondary syphilid. We have seen at least half a dozen such cases in consultation in which the physician feared he was dealing with an arsenic-fast syphilitic recurrence.

Arsenical exfoliative dermatitis is the arsenical cutaneous *bête noire* with its former 50 per cent mortality. As a clinical entity this is subsequently discussed in greater detail from the standpoint of diagnosis and treatment, but has an as yet incompletely elucidated etiology.

It is particularly true of arsphenamine cutaneous reactions and especially exfoliative dermatitis that they have a systemic background of predisposing causes, one or more of which may contribute to the production of the trouble which is provoked into explosion by the exciting cause. Among the predisposing factors must be enumerated various causes of vascular injury of the vari

ous types described heretofore which may form the anatomicopathologic basis of the arsphenamine urticarias erythema multiforme and ninth day erythema as well as dermatitis storage overload as when the skin receives an unduly large share of arsenic owing either to perverted metabolism of the drug or subnormality of the other storage depots cutaneous physiologic or functional abnormalities, such a those present in seborrhea (hypersecretion of fat) true allergies to arsphenamine a tendency to allergic reaction to irritants constituting the eczematous diathesis the sensitizing influence of circulating bacterial protein or split products from acute or chronic infection the effects of hepatic injury and possibly as Moore has suggested bone marrow injury which lowers the resistance of the patient to infections and influences hi tolerance of drugs.

Theoretical discussions ill be found in Schiff Moore and Keidel, nd Stokes and Cathcart, but are too long for full citation here In general it may be said that the major theories group themselves int allergic, infection, and arsenical schools. Cathcart and Stokes felt that the allergy as not necessarily specific for arsphenamine but recognized it as the basic fact. Moore and Keidel suggested the allergy-inducing effect of colloidal solutions of the drug. Klauder Frei, Sulzberger and others have independently demonstrated the allergy-inducing and skin-sensitizing properties of the rsphenamines as such, and the influence of these factors in the onset of dermat itis. At times the continued absorption of bacterial protein from focus of infection or sudden liberation of such proteins following flare-up in the focus (now well-recognized effect in allergic phenomena) due to arsphenamine (Milian) may be influential. Our own studies led us to suspect acute intercurrent infection as in the infectious asthmas, for example, to have marked sensitizing effect. This was particularly observable in several patients with tuberculous nodes. Milian among European uthors represents the group believing that infection, particularly of focal character is vital influence in the induction of cutaneous arsphenamine reactions. The obser vations of Lees on 86,000 injections, and those of Cathcart and Stokes and Kulchar and Stokes and Smith (1938) constitut the principal publications on the contributory influence of infection. The arsenical concepts include the suggestions of Moore and Keidel as to the vasculotoxic effect of the drug in both the skin and bone marrow The observations of E. Hoffmann, Spiethoff and of Milbradt on hepatic injury and the value of glucose and insulin and liver extract in treatment (p. 369); and the evidence of Osborne as to the accumulation of arsenic about the cutaneous capillaries and the disappearance of the drug coincidently with improvement in the dermatitis are recent contributions. Upon the basic fact of hypersensitiveness for which evidence may be found, for example in Fig 88, showing the small amounts of arsphenamine received by patients sustaining dermatitic reaction, may be superposed variety of other influences including impaired liver function from arsenic as such, which interferes with the proper metabolism of the drug as just mentioned, and impaired liver function from chronic or acute infection; subthreshold allergic shock in intolerant patients, nd the like. Damage to the suprarenals is suggested by the striking evidence of vasomotor imbalance and vasoparesis in patients with cutaneous arsphenamine reactions of the urticarial and dermatitic types. The intense itching accompanying them as suggested by Harris particularly as sign of deficiency of epinephrine and the vasodilation thus induced permits the development of the syndrome of Auer which, by permitting an increased supply of the allergen or irritant to the sensitive cells creates tissue explosion with exfoliative dermatitis in the skin nd inflammatory changes in other tissues. The role of arsenic as such, important though it unquestionably is, can hardly be regarded as indispensable or even t times as of major importance in exfoliative dermatitis as complication of the treatment of syphilis French, for example, from large experience recommends the practice of resuming the administration of the same brand and type of arsphenamine as soon as the patient is able to be up and around the ard again, his exfoliation just completed, and have seen personally examples in which this, t us highly dangerous procedure, has been carried through ithout serious results. Milian was ble to continue the administration of the same drug for number of injections after the onset of cutaneous reaction, the successive flare-ups disappearing ith the later and larger doses, situation quit inexplicable if arsenic as such and its accumulation and retention are the sole factors in dermatitic reaction (see Eighth or Ninth Day Erythema, p. 410). Here, in the field of the cutaneous toxicology of the arsphenamines, as in other aspects of the behavior of the human body under antisyphilitic treatment, complex of causes rather than any single causal element is probably operating The more recent experimental ork on arsphenamine llergy is considered on page 255

Hepatic Injuries.—Those induced by the arsphenamines are fortunately very rare at least in their acute manifestations and a good deal of confusion exists in their differentiation. The clinical aspects of this problem are discussed in Chapter IX on the control of reactions, and Chapter XVIII on the differential diagnosis of jaundice in syphilis. Hepatitis in the course of arsphenamine treatment, for this is a better term than arsphenamine hepatitis, has,

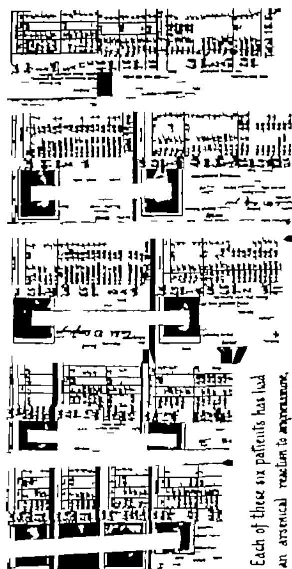


Fig. 88.—Chart hastily constructed for necropsy demonstration from clinical records, taken at random, of 6 patients who had had exfoliative reaction, including tw severe and one fatal; and 6 patients he had had really intensive treatment. All the intensively treated patients were receiving coincidently ith arsphenamine from 4 t 6 weekly injections of mercury succinimide usually 0.25 grain (0.01 Gm.) each. Most of them received coincidently sodium iodide intravenously from 2 to 20 Gm. daily None of the intensively treated patients reacted. T of the 6 who reacted had received practically no mercury

like dermatitis in all probability a complex of causes at its back. The commonly recognized forms are (1) the acute early type coming on within a few days or even hours after the injection of an arsphenamine derivative, whether the first or a subsequent injection in a series (2) the late or delayed type and (3) the acute yellow atrophy postarsphenamine. The course of the acute early type is usually benign without constitutional symptoms and terminates in

recovery though Stewart Vining and Bibby reported the case of a patient who, after an asymptomatic interval of several months following jaundice died abruptly of acute yellow atrophy of the liver The late arsphenamine jaundice is much the more serious of the two chronological types and may come on during a course of treatment, or some months or weeks after its completion The majority of these cases recover in six weeks to three months but in those with more severe onset, acute yellow atrophy is to be feared There is often enlargement of the liver but by no means necessarily Anorexia, nausea, weight loss, profound anxiety and nervous depression with the usual symptomatic concomitants of jaundice and a prodrome often of intense arthralgic symptoms are well recognized. Acute yellow atrophy may terminate either early or late cases, or appear with fulminating abruptness from a clear sky usually some weeks or months after the completion of a course of treat ment, in this respect resembling chloroform injuries to the liver Fever vomiting, chills, delirium excitement followed by coma and death may supervene in the course of an apparently benign jaundice

The various causal possibilities involved when jaundice and acute yellow atrophy appear in association with syphilis and the administration of arsphenamine include: (1) Syphilitic infection as the sole cause; (2) form of therapeutic shock due to previously existing hepatic syphilis flared up by the arsphenamine (3) rest interval relapse in the liver with the development of jaundice and other symptoms as hepatorecurrence (Milian); (4) a latent bacterial or virus infection, stimulated as result of the injection of the arsphenamine or engrafted on liver previously damaged by the drug (5) arsphenamine acting on liver previously damaged by syphilis (6) arsphenamine damaging the liver as such; (7) other disease processes which may produce jaundice.

The differential considerations involved in extricating the various items from the complex of jaundice in association with syphilis is summarized in the chapter on syphilis of the liver (Chapter XVIII, p 873)

In general it may be said that the jumble of toxic, infectious, syphilitic and surgically treatable factors in the picture of jaundice occurring in the syphilitic patient is responsible for confusion in the literature which swamps the inexperienced reader at once. Arsphenamine toxic icterus is the older and more familiar entity and having received extensive study in the early days of salvarsan it gets special emphasis in German writings. The French are divided between the Milian group who call for more arsphenamine for every case of jaundice because they interpret it as hepatorecurrence and the observers who contend that late icterus is product of arsphenamine poisoning resembling chloroform poisoning. These latter feel that damage to the liver can be demonstrated by various tests and that arsphenamine should not be used. British observers have been divided between those inclined to ascribe the entire process to arsphenamine, such as Stratby Smith and Hanson and Anwyl-Davies (1942), and other observers who have directed attention to epidemic features, notably the Cherryhinton military hospital epidemic in 1917 reported by the Salvarsan Committee of the Medical Research Council (1922) and series of cases observed by McDonald in 1918. Anwyl-Davies (1946) even contends that arsenoxide, "Mapharside," gives the lowest jaundice rate of the various arsenicals. In the United States the usual explanation of jaundice in patient under treatment with arsphenamine has been *post hoc, ergo propter hoc*. On the other hand, more attention has been given to the complicating factor of epidemic jaundice. Symmers called attention to new severe type of epidemic jaundice occurring in New York in 1920 with high mortality from acute yellow atrophy and not associated with syphilis or heavy-metal poisoning. Working with Brunsting and Lemon, Stokes pointed out that there had been an extraordinary increase in the incidence of jaundice among the patients of the Section on Dermatology at the Mayo Clinic in the years, 1919–20 which was not attributable to any change in methods of treatment. It was shown that this type of jaundice had distinctive prodrome suggesting an infectious element that it ran typical course that there was more than suggestion of epidemic background; that the process was hemolytic in character, as shown by the appearance of urobilin and urobilinogen in the duodenal contents, with restoration to normal on recovery and that it was possible in many cases to continue treatment with neoarsphenamine

throughout the course of such jaundice without the slightest ill effects from the arsenical treatment. It was, moreover, shown that the jaundice occurred in patients who had never had syphilis or treatment for it, that it followed treatment with mercury and iodide as well as with arsphenamine, and that it occurred in severe and typical forms, patients even dying from acute yellow atrophy who had not been treated for syphilis for as long as two years, whose Wassermann reactions were negative, who were free from clinical signs of activity or who never had had syphilis. A study by Blumer of the incidence of epidemic infectious jaundice in the United States clearly demonstrated the existence of an epidemic prevalence of the disease although its etiology remains obscure. A survey of cases in New York eliminated Weil' disease. Personal communications received at that time from observers on Long Island indicated that the disease may assume grave forms and be confused with surgical conditions of the gallbladder. Such cases were also observed in the Mayo Clinic and on exploration the preoperative diagnosis could not be substantiated, only diffuse hepatitis being found. Bodin published figures similar to those of Stokes *et al.* and since the publication of their conclusions, epidemics have been observed in other syphilis clinics of this country without any explanation traceable to medication or technic as such. The normal incidence of jaundice on a treatment service cannot, of course, be precisely estimated but should not exceed 1 to 1.5 per cent. Bodin incidence rose t 7 per cent. The Mekowski statistics referred to later give the incidence of jaundice as once in each 2000 injections of arsphenamine (0.80 per cent) and once in 8000 injections of neoarsphenamine. The incidence of jaundice in Stokes series by cases was 1.5 per cent of which incidence 91 per cent fell within the third and fourth of period of four years and was coincident with epidemic influenza throughout the United States. Wile and Sams (1934) reviewing the experience of the University of Michigan clinic found much evidence supportive of the conception of contributory infectious factor. Rugs epidemiologic study (1934) in the German navy is confirmatory. The recent literature on this subject has been reviewed by Stokes and Beerman (1941).

The mechanism involved in this peculiar association of epidemic infectious jaundice with the treatment of syphilis is still unsettled. Numerous writers have suggested that though arsenic may be predisposing factor the agent actually causing the jaundice and acute yellow atrophy is an organism from some intercurrent infection (virus) (Lancet, 1944). In this connection the ork of Opie should be recalled as demonstrating that in chloroform injuries to the liver much more marked and serious effects can be secured by the combination of chloroform administration and the injection of living bacteria than with chloroform alone. Hurst and Hurst have obtained similar results with manganese chloride and Bacillus coli injections. In Stokes studies of the duodenal flora of these cases no convincing results were obtained bacteriologically but there was definite evidence of duodenitis, hemolytic organisms were recovered by McDonald in the Newcastle epidemic and by Fraenkel but the results are subject to the usual criticism of bacteriological examinations made after death. Rugs incriminated the typhoid-colon group.

Hanger and Gutman (1940) have presented careful study of twelve cases of postarsphenamine jaundice in which icterus was not hepatogenous but appeared to be due to obstruction of the intrahepatic biliary tract. The clinical and pathologic features of these cases suggest distinct type of reaction to intravenous arsenicals.

Liver Function Under Arsphenamine Therapy.—The use of liver functional tests for the detection of arsphenamine damage to the liver has yielded conflicting results. Kolmer and Lucke found that even therapeutic doses of arsphenamine produced slight structural changes in the liver.

Widal, Abrami, and Iancovesco, using the hemoclasic reaction of Widal (leukopenia following the ingestion of glass of milk on the empty stomach) found evidence of hepatic insufficiency without jaundice or other overt signs eighteen and twenty four days after the end of normal course of arsphenamine treatment. Spence and Brett, using levulose test, thought they detected evidence of damage. MacKenzie Wallis believed he detected evidence of late damage rather than early. Kartamischew believed the action to be cumulative. American investigators have been less convinced that significant damage occurs. Chargin and Orgel, using the Meulengracht method for bilirubin in the blood serum, found that 17 per cent of 84 patients developed hyperbilirubinemia during arsphenamine treatment, the quantity increasing with successive injections of the drug. Schamberg and Brown applied the van den Bergh test and found no definite relationship to the amount of arsphenamine used, though they believed the test useful as guide to the resumption of treatment in patients who had been jaundiced. Greenbaum and Brown, using the Rosenthal modification of the phenoltetrachlorphthalein test (Rosenfeld-Schneider technic), found that no appreciable injury was done to the liver by considerable series of injections of the

arsphenamines. They concluded that the test ought to be performed in all syphilitic patients showing some form of intolerance to the arsenobenzenes (itching, tingling in the extremities, and mild dermatitis in particular). Icterus is too late a sign of toxicity in their opinion. Observations on the icterus index are summarized in Chapter XVIII. Irgang (1937) showed that while present day tests of liver function are of great value in detecting mild and severe grades of inflammation, they are incapable of disclosing incipient pathologic change. They are furthermore of somewhat limited value in differentiation of the various factors involved in the causation of jaundice during antisyphilitic therapy.

Personally, we believe it is very difficult to escape even the relatively weak evidence of an association between arsphenamine therapy and jaundice. It may well be recalled that Warthin gave it as an item of his autopsy experience in the arsphenamine era that hepatitis had become a common feature of practically all syphilitic patients with a history of intensive arsphenamine therapy. While it seems to us that this relation to arsenotherapy must be accepted, intercurrent infection is an important exciting cause in jaundice as it is seen at the present day in conjunction with the treatment of syphilis. The true arsenical cases are in general of the more fulminating type associated with other direct evidence of arsenical intoxication, including especially peripheral neuritis and exfoliative dermatitis, and are relatively rarely of the milder type.

Renal Injury.—This complication of the use of the arsenicals may be asserted to occur, for all practical purposes, only as the result of the administration of toxic doses or preparations. Mapharsen is stated by Levin and Keddie (1942) to be not especially nephrotoxic although two deaths due to kidney damage were attributed to its use in various reports. The urinary evidence of renal irritation occurred in one patient out of each sixty-four in their series.

While several examples were reported in the early years of the arsphenamine era (Nasta, Tucker), so that arsphenamine anuria is well recognized, its occurrence has been noted almost exclusively with the accidental administration of unneutralized or otherwise toxic solutions of "606. Its appearance as a complication automatically raises the question as to the correctness of the technic. "Extended investigations by Rappleye, Elliott and Todd, Bailey and McKay, Anderson, Weiss and Corson, Rabiro and Brown, upon the renal functional disturbances produced in man and animals by therapeutic doses of the arsphenamines using both renal functional tests and blood chemical determinations have shown that the injurious effects are practically nil. Single large toxic doses and presumably also moderate doses administered to definitely idiosyncratic individuals are, of course, another matter." Lemierre, Etienne, Bernard and Lambling have reported a case of anuria following neoarsphenamine (novarsenobillon) marked by severe pain over the kidneys and a thirty-six hour anuria. This pain over the kidneys Stokes observed in 5 successive severe intoxications with a defective brand of "606" and once with neoarsphenamine followed by albuminuria and cylindruria. In the case cited by Lemierre *et al.*, the nephrosis was hemorrhagic in character. The extraordinary tolerance of the kidney for arsphenamine is nowhere better illustrated than in the treatment of acute syphilitic nephritis in which a urine which boils solid and presents innumerable casts will clear almost immediately upon the administration of minimal initial doses of "606" or neoarsphenamine. In general in animal experimental work, at least, neoarsphenamine is, however, the more irritant preparation for the kidney. McFarland found the opposite, however, to be the case in man. Stokes has observed from time to time on the service at the Mayo Clinic the appearance of a reducing substance, in some cases undoubtedly glucose, in the urine following arsphenamine injection and absent in the interim. The patients were not subthreshold diabetics. One in particular was an elderly arteriosclerotic and another a young girl with prenatal syphilis. Whether or not the glycosuria was renal was not determined at the time. This complication is evidently rare.

Injury to the Suprarenals.—The evidence that arsphenamines seriously affects the suprarenals in the ordinary treatment of syphilis is at best tenuous. The mere good effect of injected adrenalin upon the nitritoid crisis certainly can hardly be accepted as proof.

Kolmer was unable to confirm Hirano on a deficiency of adrenalin in the blood after injections of arsphenamine. Osborne was unable to find any conspicuous concentration of arsenic in the

suprarenal cortex and believed that such evidence of injury as there is, is preponderantly vascular. In one patient Stokes had the opportunity to treat with an addisonian syndrome of the classic type apparently of syphilitic origin, the injurious effect of arsphenamine on the suprarenals was very apparent with each injection. A marked increase of pigmentation, diarrhea and profound *prostration with marked drop in blood pressure persisted for several days after each injection* but could be controlled by large doses of adrenalin per rectum and hypodermically. On giving up the use of arsphenamine and substituting mercury bichloride intravenously and later bismuth intramuscularly no ill effects were observed. At autopsy subsequently extensive damage to the suprarenals, presumably by the disease, was recognized.

Respiratory Injuries.—These follow the intravascular agglutination caused by acid arsphenamine "606" and also by the disodium salt. They also express themselves in the pulmonary edema phase of the nitritoid crisis and in the tendency to develop bronchopneumonia in the presence of acute respiratory infection when "606" is administered.

In such circumstances, and in fact, even in the absence of obvious respiratory infection, the administration of concentrated arsphenamine solution and acid arsphenamine is very apt to eventuate in bronchopneumonia, as in the cases reported by Schwerdtfeger and Tinker. De Beyrouth and Klauder have reported asthmatic wheezes associated with the intravenous injection of neoarsphenamine and with the handling of the drug in powder form, Klauder's case being in a physician who also developed a local sensitization dermatitis. Szarvas (1931) and also Saunders (1942) have reported arsenical asthma.

Arthritic reactions with swollen and painful joints occasionally occur in association with postarsphenamine febrile reactions and erythema multiforme. They are probably either the results of a flare-up in a focus of infection for which the arsphenamines have been blamed by Milian, or resemble the arthritoid manifestations accompanying certain urticarias and angioneurotic edema.

Injuries to the Blood and Hematopoietic System.—This group of arsenical by-effects now known to occur with every drug now used in the treatment of syphilis, including mapharsen, while not numerically large, is critically important because of the unpredictability, suddenness and highly fatal character of the reaction. Simple hemolysis of red blood cells apparently depends more on solvent concentration than on the drug and in modern procedures with special solvents and appropriate dilutions, is no longer of practical importance. Intravascular agglutination in a nitritoid crisis is also without clinical importance. The serious reactions to the arsenical drugs are classifiable under the broad category of conditioned toxic injuries, ably discussed by Fitz Hugh (1938) as the result of a wide variety of insults to the bone marrow produced by infections, drugs, allergens, cyclic factors in women, the fatigue state, perverted metabolism and deficiency states. The relative importance of arsenic and the benzol ring in these reactions to the arsphenamines remains undecided, but clinical experience clearly shows that the process of sulfonation in the manufacture of arsphenamine produces compounds such as sulfarsphenamine which have a markedly higher incidence of bone marrow injury than do the other types of arsenical. Stokes's experience with a patient suffering from aplastic anemia and repeated attacks of thrombocytopenic purpura who was nonetheless able to tolerate without difficulty the intravenous use of sulfarsphenamine, indicates the highly specific character of the injurious effect. The very minute amounts of the offending drug capable of producing it have been demonstrated by Epstein and Falconer and they showed furthermore that successive reactions lead to increasing sensitiveness to the drug, so that repetition of treatment after evidence of thrombocytopenia has developed is definitely and indeed exceedingly dangerous. Caletti (1940) and Brunet, Shaw and Reinhardt (1941) showed that the concurrent administration of an arsenical and other drugs such as the sulfonamides which can produce hematopoietic reaction did not increase the intrinsic risk from either alone.

Classifications of the types of bone marrow injury range from McCarthy and Wilson's four subdivisions of thrombocytopenia thrombocytopenia and granulocytopenia agranulocytosis and agranulocytopenia, and aplastic anemia to Burke's simplification into two types including thrombocytopenia and granulocytopenia. Actual cases are probably much more frequent than the reported incidence suggests, many being lost under such headings as purpura, agranulocytic angina, aplastic anemia, leukemoid reaction and arsenic poisoning. Burke's estimate based on the experience of the Whitechapel Clinic, approximates 0 4 per cent of treated patients, but the fact remains inescapable that a large clinic may operate for years without the occurrence of a single case. Aside from the factor of drug selection there are probably conditioning elements, as Fitz Hugh indicates, including intercurrent infections, pregnancy and so forth, which abruptly step up the incidence under special circumstances and at special times The destruction of blood platelets is the primary clinical and pathologic fact, and upon it ensue the purpuric hemorrhages which are often the earliest clinical signs. Dodd and Wilkinson pointed out, however as have other authors, that in cases tending to the granulocytopenic type of reaction with the development of aplastic anemia, thrombocytopenia may not appear early or even at all and the patient go on to profound destruction of the bone marrow with or without regeneration and the development of a fatal aplastic anemia which would only be recognized by blood studies for which at first there would be little symptomatic indication. Moore and Foley especially emphasized that stomatitis and dermatitis, quite as much as purpura, should be the signal for an immediate blood study and the appearance of immature cells should be a warning to discontinue arsenical treatment or to proceed with the greatest caution. The relative immunity of childhood and of the young, healthy specially favorably conditioned adult represented by the personnel of the United States Navy to aplastic anemic complications following the use of the most hematopoietotropic drug sulfarsphenamine is yet to be explained. Possibly relative freedom from focal and serious conditioning infections, adequate diet and vitamin intake, and similar as yet unevaluated influences are important. Vitamin C, however which has been employed in large doses by Epstein and Falconer was without effect after the thrombocytopenic reaction had developed

A drop in red blood cell count may precede, accompany or follow the fall in leukocytes and may reach astonishing figures before death supervenes. The lowest reported leukocyte count in the Dodd and Wilkinson series is 136 the lowest recorded red blood cell count 80,000, and the lowest hemoglobin, 13 per cent. The lowest platelet count, reported by Gorke, was 10,000. The purpuric hemorrhages and the necroses which develop about the teeth, gums and tongue and which lead to confusion with agranulocytic angina of the idiopathic type are of course, secondary manifestations due to the activity presumably of mouth flora and "opportunistic bacteria (Fitz-Hugh) unleashed by the drop in leukocytic defense. An abrupt onset of pneumonia following stomatitis may be the first warning of the gravity of the patient condition if blood-counts have not been previously taken

Allergic Reactions to the Arsenicals.—The study of allergic reactions to the arsenicals has made rapid and in some particulars paradoxical and puzzling progress during the past several years True tissue hypersusceptibility is thus far definitely known only for the respiratory tract and the skin. It seems possible that the intestinal mucosa may react in this way in certain otherwise unexplainable examples of intolerance.

By far the most important aspect of hypersusceptibility and allergy in

ordinary treatment work is cutaneous sensitivity to the arsenicals. This fascinating subject still in process of experimental and clinical development, gives some promise of yielding a safe procedure for determining whether or not a patient who has once shown a dermatitic reaction to an arsenical can continue this form of treatment. The following is a brief résumé of present knowledge.

It seems probable from the investigations of Jadassohn and Bloch that urticarial and eczematous reactions in the skin must be sharply distinguished from the standpoint of the allergies involved. The eczematous manifestations are particularly examples of intrinsic cutaneous rather than vascular sensitivity and it is these which are of the more importance in dealing with the arsphenamines. Bloch succeeded in showing in his experimental work on the toxin of primrose that direct introduction of powerful sensitization-inducing substance into the skin was capable of sensitizing even normal persons. Klauder one of the first American students of the subject showed in 1920 that there was disconcerting intimacy of connection between exfoliative dermatitic reactions in patients and the previous occurrence of intradermal injection of an arsphenamine through technical error resulting in tissue leakage around an improperly entered vein. Klauder observations have since been confirmed, especially by Nathan and Munk, and by Frei, who have also recognized flare-up reactions at the sit of intradermally injected arsphenamine when patients subsequently received intravenous injections of the same drug. Moore *et al.* Shaffer (1934) Stokes (1934) Cormia (1941), E. Epstein (1937) and others on the other hand, could not notice ny conspicuous association between instances of arsphenamine leakage and subsequent onset of dermatitis. The observations just cited, together with those of other observers, have, however led t definit tendency t discourage the ttempt to test for arsphenamine sensitivity by any procedure hich outright breaks the surface of the skin and introduces the drug to the deeper epithelium. Unaware, of course, of these observations, which followed them by a number of years, Klauder had employed scratch test and Stewart and Maynard had employed intradermal injections of dilut rsphenamine solutions in the effort t determine whether or not patients ere sensitive cutaneously to the arsphenamines. Frei (1928) produced skin sensitivity t neoarsphenamine (Hoechst) in guinea pigs by angle intracutaneous injection. No anaphylactic shock was observed in these animals after intracardiac reinjection. Attempts to sensitize other animals such as dogs and rabbits gave negative results. Sulzberger (1929–1930) stated that the sensitivity to neoarsphenamine (Hoechst) can be induced and demonstrated only in the skin and that the skin sensitization could be inhibited if an intracardial injection was given twenty-four hours after the intracutaneous preparation, but desensitization could not be induced by an intracardial injection hen given after the hypersensitivity had developed. Sulzberger and Mayer (1931) in animal experimental studies, conducted at the Jadassohn clinic in Breslau and later in New York, obtained in their earlier ork what appeared to be definite evidence of sensitization of guinea-pigs by intradermal injection of arsphenamine. T their surprise, however these results did not prove susceptible of satisfactory repetition under different physical conditions and geographical location, so that the whole subject was to some extent throw into confusion. One of the factors responsible for these differences was the diet of the animals in that green fodder inhibited and dry fodder favored sensitization. Sulzberger and Oser (1934) observed for the first time that the amount of vitamin C in the diet had some definite influence on sensitization, large doses having an inhibitory effect. I 1934 Sulzberger and Simon found differences in the incidence nd degree of sensitivity in New York as contrasted with Boston. They in conjunction with Williamson and Morrell, showed that the degree of hypersensitiveness depend also upon the brand of the neoarsphenamine employed since certain lots of arsenicals have high sensitization index. They demonstrated that guinea pigs are in general specifically sensitive to the arsenobenzol complex and not to other trivalent or pentavalent organic and inorganic arsenicals although subsequent reactivity to pentavalent arsenicals may develop as rare example of polyvalent sensitivity (Epstein, 1937 Golz, 1939; Franks and Fisher 1940) Cormia (1941) pointed out that the more complex trivalent arsenicals are much likelier to cause dermatitis, while arsenoxide is incapable of producing sensitization in animals since it has low sensitization index. Frei (1937) orking on guinea-pig sucklings, studied the question of why infants do not acquire neoarsphenamine exanthemata. Animals one week old showed absolute resistance to sensitization. This resistance gradually disappeared as the animals grew older. The findings of Frei and Sulzberger have been confirmed by numerous investigators (Kaplan and Moreinis, 1930 Kapuściński, 1930 Ma, 1938 Sézary *et al.*, 1933; Streitman and Wiedmann, 1937 Chapman and Morrell, 1935 Cormia, 1936, 1937.) Mayer (1931), Kallós and Kallós-Deffner (1933) and Cormia obtained different results on studies on the allergic nature of arsphenamine dermatitis utilizing the Schultz-Dale test on the isolated guinea-pig uterus. Cormia, for example, obtained completely negative

results. The relationship of intercurrent infection and dietary factors in arsenical sensitization is fully discussed on pages 369 and 372. Landsteiner and Jacobs (1936) obtained, after intracutaneous injection of dilute unneutralized arsphenamine solution, a high degree of skin hypersensitiveness in practically all injected animals. When such sensitized animals were given neutralized arsphenamine 606 solution intravenously a considerable percentage died in typical anaphylactic shock. This shock occurred more regularly and was more severe when the solution was mixed with guinea-pig serum. These experiments definitely indicate that arsphenamine, a simple chemical, nonprotein, is capable both of producing skin hypersensitivity and of producing anaphylaxis and anaphylactic shock. This method also gives regular and definite results. Frei and Sulzberger (1936) using this method found that arsphenamine 606 regularly produces cutaneous sensitivity to itself as well as to two brands of neoarsphenamine. Intracutaneous injection of arsphenamine 606 generally produced anaphylactic sensitivity to arsphenamine 606 but not to the neoarsphenamines. Frei (1941 1942) showed that guinea-pigs sensitized to arsphenamine did not exhibit increased susceptibility to sensitization to other drugs (quinine hydrochloride, acetyl salicylic acid, barbital). He found that the skin sensitiveness of sensitized guinea-pigs was directed against aromatic arsenicals in general and not against arsenic nor exclusively against arsphenamine. An effort was made by Fuhs and Riehl to demonstrate the passive transference of arsphenamine sensitivity to normal persons, the methods employed including intradermal injection of blood serum from a hypersensitive patient (Prausnitz-Küstner method); intradermal injection of vesicle fluid, and so forth. Ensbruner has apparently accomplished passive transfer with blood serum. The successful induction of passive transference in some of these cases has been questioned by Schoch as being due probably to transference of minute quantities of arsphenamine to the skins of the normal subjects, rather than to any actual transfer of sensitivity. In any event, these methods, together with the percutaneous or intradermal introduction of arsphenamines into the skin by hypodermic needle or scarification are at present deprecated as probably dangerous and likely to induce sensitivity if not already present.

Much hope was placed in the method of patch testing devised by Jadassohn and employed in this country recently by Chargin, Sulzberger and Crowley and by Schoch. Robinson (1936), Jordan and Osborne (1933), and Beerman (1936). In a considerable series of tests performed at the University of Pennsylvania Clinic Schoch, for example, succeeded in showing that the arsphenamine factor in induced sensitivity to a double salt such as bismuth arsphenamine sulphonate could be detected by the patch test and that the test be of very considerable value, though not absolutely infallible in the detection of significant degrees of cutaneous sensitivity and risk of arsphenamine dermatitis (Jordan and Osborne, 1933 Beerman, 1936; Bechet, 1939). Routine patch testing may induce sensitivity in some persons. Beerman has apparently observed such a case on our service (1933).

From an extended study of the arsenical patch test, we, as well as Robinson, have concluded that the patch test is not specific enough to be implicitly relied upon as an advance indicator of arsenical sensitization since a patient with a negative patch test may develop arsenical dermatitis on further administration of arsenicals and vice versa. It has failed as a reliable means of detecting the specific allergic factor in a cutaneous reaction other than typical arsenical dermatitis occurring during arsenical treatment. It may not be entirely harmless. Because, in the hands of experts it may serve as a guide to further treatment, especially with arsenoxide (Schoch 1940) we are detailing the technic of this test.

The technic of carrying out the patch test and the method of reading and interpreting the results, may be summarized as follows (Schoch). 0.3 Gm. of neoarsphenamine is dissolved in 1 cc of distilled water. Bismuth arsphenamine sulphonate solution of the same concentration may be used as the test solution where this drug is suspected. Mapharsen patch tests are performed with 3.3 per cent solution. A small linen patch is saturated with this test solution, applied to the intact skin of the arm and covered in turn with tracing cloth, bound down at the margins to form an airtight chamber by adhesive tape. At the end of twenty-four hours the patch is removed and the first reading made. A strongly positive reaction consists of an acute dermatitis at the test site, with vesiculation, as shown in Fig. 99. Partial positive reactions that show only erythema and a few papules are not regarded as evidence of definitely established cutaneous hypersensitiveness to the arsphenamines, only pronounced dermatitic reactions being regarded as clearly positive. After the inspection of the patch site twenty-four hours after application, the impervious dressing is removed and the test site reinspected about one-half hour later at the end of which time strongly positive reactions sometimes develop on exposure to air. The test site should be reinspected forty-eight hours and even a week after the impervious dressing is removed to recognize the last trace of a delayed positiveness. The test site of a strongly positive reaction usually returns to normal in about three weeks. Strongly positive patch tests with neoarsphenamine are interpreted as showing too high a degree of cutaneous hypersensitiveness to permit

further arsphenamine therapy Negative patch tests, on the other hand, were assumed by Schoch to permit cautious attempts to continue arsphenamine therapy usually with some other form of this group of drugs tha that previously employed

In conjunction with this work, Schoch performed series of experiments indicating a practical haza d in arsphenamine work and coincidently the extremely minute amounts of the arsphenamines which are capable of inducing sharp dermatitic sensitivity reactions in susceptible patients.

Using the Lloyd and Lloyd modification of the Abelin test, he showed that even on syringes used for the intramuscular injection of an arsphenamine after they had been rinsed and boiled in ter for adequat sterilization, there still remained sufficient traces of arsphenamine, extremely minute though they must have been, to induce sensitization reactions in patients previously known to be sensitive to the arsphenamines. Thu a bismuth suspension given in syringe previously used for bismuth arsphenamine sulphonate and cleansed only by rinsing and sterilization is capable of inducing an exfoliative dermatitis due to arsphenamine in patient previously sensitive to the arsphenamine group of drugs. It is necessary to clean syringes used in such work with soap, water and cotton swabs, t insure the protection of sensitive patients.



Fig 89—A positive patch test with neoarsphenam ne, in patient sensitive to the drug The erythematous plaque is studded with vesicles.

While variety of theoretical considerations, including the extreme difficulty of interpreting intradermal test procedures involving necrosis-inducing substances and colloids, are involved in the earlier test method and have brought them into discredit both on the score of trustworthiness and safety it seems very probable that considerable measure of reliance, though not unqualified, may be placed on the result of the patch test as above described i deciding upon the fitness of patients for further arsphenamine therapy once dermat tic reaction has occurred It should be stated, however that conservative observers, Klauder for example, have expressed themselves as strongly opposed t any attempt t continue any arsphenamine therapy whatever in patient who has once shown a severe dermatitic reaction in treatment for syphilis. Certainly in many aspects of the disease this stand is *absolutely justified and the only period in which we feel any* inclination to continue the use of arsphenamines if patch test results permit is in the treatment of early syphilis, where the issue of infectiousness and radical cure is involved as at no other stage *of the disease.* I such cases cautious trial of arsenoxide (mapharsen) may be considered as possible saf procedure (Schoch 1940)

Procedure after Patch Tests.—The degree of specificity involved in the arsphenamine sensitization reactions is undoubtedly considerable but not invariably absolute Thus, Cole found that two third of his patient ho had had arsenical complication could continue arsenical

treatment cautiously and of those who had had two complications, 28 per cent could continue arsenical treatment. Moore *et al.* showed that the allergic state of the hay fever subject materially influenced the severity of his reactions to intracutaneous test, thus suggesting that this factor may materially affect the onset of arsenical cutaneous sensitivity. Following negative patch tests in patients who have been suspected of cutaneous hypersensitivity or about 3 months after recovery from dermatitis, no larger dose than 5 mg. of the least reaction-producing drug available (sulpharsphenamine, arsphenamine "606," neoarsphenamine, bismuth arsphenamine sulphonate and mapharsen produce cutaneous reactivity in about the order named) should be employed in resuming treatment in a given case. At the first sign of intolerance arsenical treatment should be permanently stopped (intravenous testing, Robinson, 1936).

Sulzberger's protection of animals by intracardiac injection following cutaneous sensitization by an arsphenamine has led to the suggestion that in any case in which leakage occurs about a vein during an arsphenamine injection, a determined effort should be made to complete the intravenous injection in order to protect the patient against the development of sensitiveness. Mayer has reported the onset of the eruption in exfoliative dermatitis at the site of arsphenamine leakage around a vein. The precise applicability of this conception to man, in view of its uncertainties in animals, is undetermined, but it furnishes a useful practical maxim for the treatment room: If leakage occurs, withdraw the needle but attempt to complete the injection by entering some other vein. At the present time there is no known method of cutaneous desensitization to the arsphenamines applicable to man.

Idiosyncratic Reaction to the Arsenicals.—If the term idiosyncrasy be accepted in a broad sense as including toxic and injurious responses to the improperly metabolized drug even though we are as yet unfamiliar with the steps involved in the various processes, idiosyncrasy to the arsenicals exists but is fortunately comparatively rare. In this group should be included encephalitis hemorrhagica, for example, which is a totally unpredictable accident, fulminating acute yellow atrophy definitely traceable to the arsenicals alone, explosions of exfoliative dermatitis following the first or the first two or three injections of an arsenical despite reasonable precaution and proper dosage, hemorrhagic disease and aplastic anemia associated with special susceptibility of the bone marrow or the endothelium of blood vessels, both structures known to be markedly susceptible to arsenical injury in certain cases. Emphatic protest, however, should be registered against the all too prevalent disposition to blame accidents and complications following the administration of the arsenicals upon a hypothetical idiosyncrasy upon the part of the patient. Technical error and unfamiliarity with modern knowledge of the proper use of the arsenicals form the basis of a large proportion of pseudo-idiosyncrasies. The technical means of avoiding reaction are discussed in Chapter IX, but it is obvious from what has been said thus far that the correct technical preparation of the drug for injection, a proper rate of injection in intravenous medication and proper preliminary attention to the patient in the matter of examination and appraisal, are the chief preventives of alleged idiosyncratic reaction.

Certain constitutional states are recognized as predisposing toward idiosyncratic responses. Among these should be included profound constitutional disturbances involving infections and intoxications, conditions involving severe grades of vascular injury such as alcohol and lead poisoning and diabetes, skin hypersensitivity, pregnancy and the thymicolymphatic state. Serious disease of or injury to the liver as the principal metabolizing station in the administration of the arsenicals also contributes definitely to idiosyncrasy. Figure 90 itemizes in more detail "the seven bads" and outlines the background against which reduced tolerance, expressing itself in pseudo-idiosyncrasy, is projected. A large proportion of idiosyncratic accidents strike

the central nervous system and the skin In the former case they are most frequently assigned by the puzzled and disturbed medical attendant to the

Fig. 90.

REDUCED TOLERANCE TO THE ARSENICALS—"THE SEVEN BADS"

1 Bad brains and cords—acut meningeal and diffuse encephalitic processes, serious vascular involvement, myelitis.
2. Bad livers—early acut diffuse hepatitis, extensive late hepatitis and cirrhosis.
3. Bad spleens—cirrhotic splenomegalies.
4 Bad vascular systems—myocarditis, coronary lesions, conduction lesions, aneurysms, markedly febrile subacut bacterial endocarditis.
5 Bad lungs—advanced tuberculous nd septic processes, especially if febrile. Acut bronchitis.
6. Bad kidneys—chronic nephroses and lat interstitial nephritis.
7 Bad skins—eczema, especially seborrheic history of cutaneous hypersensitiveness, personal or familial, previous dermatitis, urticaria (chronic).

A Contraindication May be Relativ Not Absolute, and Controllable by Skilful Management.

category of Herxheimer reactions or therapeutic shock with which, of course they may easily be confused, for the distinction between a focal or diffuse

Fig. 91

A SCHEMATIC SUMMARY OF THE ARSENICALS IN CLINICAL PRACTICE

Arsphenamine Proper ("606")

Advantages.	Disadvantages.
The standard of comparison. Generally acknowledged therapeutic superiority	Cross mortality higher than neoarsphenamine
Lowest incidence of relapse, especiall neurorelapse in early syphilis, if used ith mercury or bismuth.	Dermatitis higher than neoarsphenamine but less than silver and sulpharsphenamine.
Most marked effect on blood Wassermann.	J undice more frequent than with neoarsphenamine.
Most rapid response ith fewest injections	Minor reaction higher than with low doses of neoarsphenamine, but only slightly higher ith therapeuticall equivalent doses.
Prolonged effect.	Technicall more difficult slow and cumbersome
No more immediat reactions than eaker preparations, if used in therapeutic equivalence	Hemolytic
Stability under market conditions.	Agglutinates red blood-cells in large doses (disodium salt)
Comparative st bility of solutions.	Hard on the lungs.
Uniform toxicit	Harder on the liver than neoarsphenamine.
Dependable nd uniform in therapeutic effect.	More irritant t veins. Less desirable in one-vein patients, infants, t
Better tolerated by the kidney than neoarsphenamine.	

Herxheimer reaction in the brain and a true encephalitic reaction to the drug is sometimes drawn with the greatest difficulty The presence of anything suggesting an appropriate background for idiosyncratic reaction calls for the

very greatest conservatism in initial dosage which should be not more than one fourth or one third the normal for the adult by weight. A drug should moreover be selected which is least injurious to the group of structures most involved in accordance with the principles set forth in Figs. 91-94

Therapeutic Shock and the Arsenicals.—While perhaps not properly regarded as a toxic manifestation of the use of the arsenicals therapeutic shock and the so-called "Herxheimer flare-up" are so general and in fact so almost a physiologic part of the pharmacological action of this group of drugs that a physical description is in order at this point.

The Herxheimer reaction under the administration of the arsenicals is best illustrated by a series of figures. It has a focal and a systemic phase but so far as is known no local reaction occurs at the site of injection such as is observed

Fig 94.

A SCHEMATIC SUMMARY OF THE ARSENICALS IN CLINICAL PRACTICE

Neoarsphenamine

Advantages.	Disadvantages.
Specially high-grade lots almost equal arsphenamine. Average is second best.	More relapses. Low therapeutic efficiency in the doses often used.
Very low mortality in doses up to 0.6 gm	As many complications as arsphenamine when used in therapeutic equivalence.
Dermatitis rare in low doses.	More apt to produce injury to the blood and blood-forming organs and cerebral vessels than arsphenamine (aleukemia, encephalopathy)
Jaundice rare in low doses,	Less effect on Wassermann than arsphenamine
Less toxic for liver than arsphenamine	More irritant to kidney than arsphenamine.
Non-hemolytic	Unstable in solution.
No pulmonary by-effects.	Slight errors in technic markedly increase toxicity (shaking, standing).
Marked tonic effects.	Marked deterioration possible under market conditions (also tropics)
Best tolerated by the weak, debilitated, cachectic very young, and very old patient.	Therapeutic efficiency variable and may often be low and even nil without warning to user
Safest to begin with if in doubt as to tolerance	Larger number and more frequent injections required.
Less irritant to tissues and veins	
Suited to ambulatory technic.	
Convenient to give little apparatus, small amount of solvent.	

in the use of tuberculin, whose relation to the immunology of tuberculosis bears no resemblance to that of arsphenamine in syphilis. The focal phase of therapeutic shock reaction under arsphenamine is well illustrated in the extra genital chancre in Fig 95 and consists of increased swelling redness and discharge where such was originally present. Note that the satellite bubo as well as the chancre is involved All other syphilitic lesions in the patient's body are similarly affected. The reaction develops within eight to twelve hours after intravenous injection upon an acute syphilitic process in an easily penetrable tissue and then rapidly subsides It is seldom repeated with a second injection. In fact, if it is repeated, it suggests underdosage and inefficient drug or a resistant strain of organism Stokes has seen three definite Herxheimer reactions following three neoarsphenamine injections in a secondary eruption

which cleared very slowly In processes which are difficult of access (i. e tissues of low vascularity or those which like the nervous system are relatively impenetrable to the arsphenamines) the local Herxheimer reaction is delayed and may not reach its height for days or even several weeks after the treatment is begun An example of the delayed Herxheimer in osseous syphilis showing clearly the increased swelling and discharge is given in Fig 96 Objective evidence of the occurrence of the therapeutic shock reaction in the meninges,

Fig. 95.

A SCHEMATIC SUMMARY OF THE ARSENICALS IN CLINICAL PRACTICE

Sulpharsphenamin

Advantages.	Disadvantages.
Therapeutically between neo- and arsphenamine. At least equal t neoarsphenamine.	Clinical status not fully established.
Suited t intramuscular use	Higher incidence of dermatitis.
High penetration of the nervous system.	Tendency to serious injury to vascular system as in aleukemia hemorrhagica.
Action on resistant blood Wassermann and neurosyphilis, by intramuscular root *better than neoarsphenamine*	Effects less lasting than arsphenamine(?)
	Larger number and more frequent injections.
Avoidance of Herxheimer effects t some extent by slower bsorption.	Question whether it should be used at all in adults because of reactive qualities.
Very stable under market conditions.	
Solution very stable.	
Low animal toxicity	
Few immediat reactions.	
Technic of administration as simple as neo- or simpler (intramuscular)	

Silver Derivatives

A new angle of ttack on resistant cases.	Higher incidence of dermatitis.
Efficiency higher than other drugs in proportion t arsenic content, but mid y between arsphenamine and neoarsphenamine in dosage used.	Possibility of argyria.
Apparently less vascular disturbance in serious organic lesions.	Higher incidence of immediate minor reactions.
	Less effect on Wassermann than either neoarsphenamine or arsphenamine
	Question if mercury or bismuth should be used simultaneously
	Little know of selective or special action.
	Dose must be small t void trouble.
	Technically d fficult (saline necessary dark solution)
	More expensive tha arsphenamine

delayed as might be expected by the impermeability of the tissues, is seen in Fig. 97 in which the rise in cell count s an index to meningeal reaction shows a definite curve upward through a period of days before its final reduction to normal

The importance of the focal phase of the arsenical Herxheimer reaction is proportional to the location and physiologic importance of the tissue in which it arises. This fundamental principle deserves and has received repeated emphasis in the foregoing discussion

A Herxheimer reaction i the tibia is seldom significant A Herxheimer reaction in the larynx, here the tissue per se is not likely t suffer serious damage by the flare-up is, however of vital importance because the edema may close partly cicatricized passage completely with result ing asphyxiation if help is not at hand. A Herxheimer reaction in the wall of an aneurysm, due

Fig. 91

A SCHEMATIC SUMMARY OF THE ARSENICALS IN CLINICAL PRACTICE

Mapharsen (Arsenoxid)

Advantages.	Disadvantages.
Pure crystalline form soluble in neutral, acid, or alkaline solutions.	Not sed long enough t determine per manence of results.
Practically complet freedom from produc ing nitritoid reactions.	Best effect require t or more injections per eek.
Greater therapeutic effect ith smaller doses of arsenic	May produce kidney or gastro-intestinal irrit tion,
Oxidation (aeration) does not increase toxicity	Inferior t neoarsphenamine in treatment of syphilis in pregnancy
May be injected rapidly	Pain along shoulder relatively frequent.
Intramuscular injection possible	Chemotherapeutic index nee 1(?)
Lowest cutaneous toxicity and general re action incidence of any trivalent arsenical.	
Adaptable t foreshortened treatment schemes.	
May be used, with caution, in patients not tolerant of the arsphenamines.	
Less disagreeable taste	

to the unintelligent use of an arsphenamine, may weaken the wall enough t cause rupture following the first or second injection (Fig. 713), and in the liver may result in a sudden portal obstruction with increased ascites that may be serious (Figs. 676, 677)



A B

Fig 85 —The effect of therapeutic shock (Herxheimer) upon a chancre of the lip. A shows the lesion on the upper lip before and B show it t elve hours after the first intravenous injection of 0.3 Gm. arsphenamine Note the local edema of the lip, the ccentuation of the lesion itself the enlargement of the satellite bubo below the left ramus

The ystemic phase of the therapeutic shock following arsenicals is rarely serious unles the grossest overdosage has occurred It may create a temporary impression that the patient is gett ng worse It is usually accompanied by

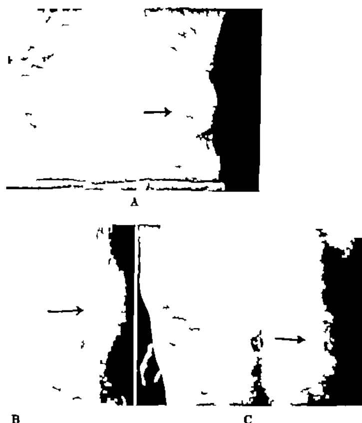


Fig 96 —Three stages in the course of gumma of the ribs under treatment showing the delayed Herxheimer reaction in bone gumma. A, The swelling before treatment was begun. B, Great increase in swelling and discharge produced by the first three arsphenamine injections (Herxheimer reaction) C, End-result after four months. Complete healing. A surgical exploration at the height of the Herxheimer reaction had failed to disclose any signs of tuberculosis or malignancy (See case history Fig 617)

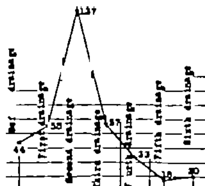


Fig 97 —Lymphocytes in spinal fluid of patient at the outset of treatment showing Herxheimer like curve

fever (Fig 98) if the spirochetes are abundant or the process active The chart here shown is characteristic of the reaction in early syphilis. Systemic response usually occurs with the first injection and in the days when sharp distinctions

were drawn between cases eligible for the so-called "abortive cure" and those in which the infection was regarded as general, considerable prognostic significance was attached to it. If the patient was serologically negative on the blood when his primary lesion was first diagnosed and treatment begun, the occurrence of fever in the twenty four hours after the first arsenical injection was regarded as indicating that his infection was general and abortive cure impossible. It is now, of course, entirely clear from the immunological consideration discussed in previous chapters that no such method of estimating the status or progress of an early syphilitic infection is justifiable. It often happens that in the primary stage a patient who, on examination, shows no signs of a secondary eruption will on the day following his first arsphenamine injection be found to have a definite roseola. To the extent that this constitutes objective confirmation of the syphilitic character of the previous manifestations it has value in diagnosis but its value is not so great that it is ever permissible to give an injection of an arsenical to a patient with an undiagnosed genital lesion suspected of being a chancre in the hope that he may develop a sec-

TEMPERATURE

No. I Dr. W.H.G.

No. II Dr. W.H.G.

No. III Dr. W.H.G.

No. IV Dr. W.H.G.

AB 3 gm

AB 5 gm

AB 6 gm

AB 6 gm

Fig. 98.—The febrile reaction in therapeutic shock (Herxheimer) following the first injection of arsphenamine (0.3 Gm.). The height of reaction was reached eight hours after injection (disregard upper numerals). This patient had a primary lesion on the index finger with a positive blood Wassermann reaction and positive darkfield, but no signs of secondary eruption. Note that no fever followed any subsequent injection.

ondary eruption as a diagnostically confirmatory Herxheimer or therapeutic shock phenomenon.

It is not infrequently observed that patients serologically negative on the blood on the day preceding the first injection of an arsenical become seropositive from twenty-four to seventy-two hours later. While this need not necessarily be labeled a Herxheimer effect, it is clinically important as indicating that the patient properly belongs in the treatment classification of seropositive primary syphilis as distinguished from the prognostically more hopeful seronegative primary syphilis. This will be reemphasized under the treatment of early syphilis.

On the other hand in late syphilitic lesions the therapeutic shock reaction may have at times definite diagnostic value and it is well worth while to include observation for focal reaction following a single moderate dose of arsphenamine among the diagnostic criteria in therapeutic test. No provocative test with an arsenical should therefore ever be given to a patient with an observable lesion without making arrangements to see the patient on the two

days following the injection to detect any focal flare-up and without watching the temperature during the twenty-four hours following the provocative injection While the therapeutic shock often fails to reach visible proportions, when it does, it is a considerable aid in piecing together the evidence in a doubtful case If the initial arsenical dosage be made large enough, therapeutic shock reactions of any grade of severity may occur Not a few of the terrific reactions with high fever great prostration and subsequent alleged idiosyncratic reactivity to the arsenicals were observed in the early days of intravenous arsphenamine treatment, and are still seen at the hands of the inexperienced who employ maximum adult doses of 0 6 and 0.9 Gm. of neoarsphenamine for example, for the initial injection. Such high dosage brings out the worst effects of therapeutic shock with no advantage to the patient, with definite disadvantage from injury to his physiologic reacting power when low dosage would have kept the flare-up within safe limits.

Symptomatic Therapeutic Shock.—This term applies to an increased severity of symptoms as distinguished from visible signs. Following the use of the arsenicals it is limited practically to the late manifestations of the disease especially in the cardiovascular and nervous systems, and rarely complicates either diagnosis or treatment in the early stages of the infection where symptomatic favorable response is usually almost immediate.

Nonspecificity of Arsenical Therapeutic Shock.—The Herxheimer flare-up following the arsphenamines is not an absolutely specific reaction and has been observed following the administration of the arsphenamines in tuberculous subjects with both focal and local processes It also occurs in other spirochetoses susceptible of treatment with the arsphenamines and Stokes personally noted it in sodoku or rat-bite fever

Arsenic Resistance (Arsenic-fastness) —This has already been sufficiently discussed under the general consideration of drug-fastness in syphilis, of which arsphenamine resistance is the most familiar example (p. 146)

Ocular Lesions Produced by Arsphenamines.—The rôle of the arsphenamines in the production of ocular lesions has been discussed in the masterful study by Zimmermann. Subsequent reports have merely added examples to Zimmermann s classification. These injuries fall into three classes (1) True toxic reactions, as conjunctival hyperemia, transient myopia, retinal hemorrhages chorioretinitis, corneal necrosis and keratitis associated with exfoliative dermatitis (Kirby 1930 Hyde 1931 Chan 1912) (2) Ocular therapeutic shock or Jarisch-Herxheimer reaction with serious consequences following in an extensively diseased eye All types of uveitis and choroid involvement may be aggravated. Interstitial keratitis is rarely aggravated while the danger in optic neuritis and tabetic optic atrophy of a Herxheimer reaction may be serious Ophthalmoplegias rarely occur as a therapeutic shock reaction (3) Neurorecurrences or iridorecurrences. Ocular lesions following insufficient treatment of early syphilis as part of a neurorecurrence (oculomotor) or as an iridorecurrence With increased knowledge of treatment these reactions have been reduced almost to nil although Skirball and Thurmon (1935) report that 2.7 per cent (20 cases) of their patients with early syphilis developed severe ocular reaction from trivalent arsenical. We recall no such complication among *our patients The prevention of these lesions depends on intensive prolonged* and systematic treatment of early syphilis.

Rate of Action of the Arsenicals.—To those who are familiar in memory with the leisurely involution of active syphilitic lesion under the treatment

of mercury and iodide days the term "arsphenamine miracle is no exaggeration (Fig. 90) Syphilids requiring months for involution disappeared in weeks and few weeks, at that. The physiologic involution of the chancre which ranged, according to the size of the lesion, from three weeks to three months excluding the disappearance of induration, was reduced by the arsphenamines to a matter of one to three weeks. A late syphilid covering the entire thigh of a woman healed completely in five weeks. Figure 90 graphically presents the really astounding effect of an active arsphenamine on destructive late lesions The rate of healing of lesions is to some extent a check upon the efficiency of an arsphenamine product and for that reason it is well worth while for the practicing physician to watch the involution of chancre and secondaries and if the average primary has not healed over in three weeks, or papular secondaries disappeared leaving only pigmentary traces, by the fourth or fifth injection, he can afford to question his dosage scale or the efficiency of his drug. On the other hand, with the increasing tendency to use the arsphenamines synchronously with bismuth such a test becomes much less significant.

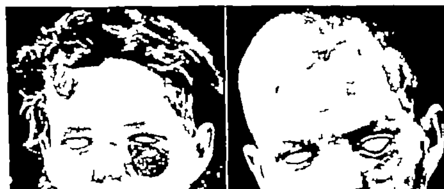


Fig. 90—An illustration of the rapidity of action of arsphenamine. Healing of two large rupial ulcers by tw injections of 0.5 and 0.4 Gm. at eekly intervals The photograph was taken on the fourteenth day before the third injection

The arsphenamine miracle extends to the symptomatology as well as the signs, and the disappearance of severe osteocopic and periosteal pain, cephalalgia, and other acute symptoms within twenty four hours after a therapeutic dose of "606" or even "914" had become a commonplace

The therapeutic miracle of the arsenicals, welcome as it is to physician and patient, is a not wholly unmixed good. The immediate recession of the disease into invisibility produced in this way leads too often to underestimation of its seriousness by the physician, shortening of the empirical maximum which experience has now shown to be essential for "cure" and desertion of the treatment regimen by the patient just at the time when it should be receiving his most assiduous and devoted cooperative attention. It will interest students of the arsphenamines to know that the American Cooperative Clinical Group studies in early syphilis showed clearly that under standard systems of treatment the largest part of the reversal of blood serological tests in primary and secondary syphilis (Chapter XIV) is dependent on the arsphenamines and in fact is carried through by the arsphenamines largely unaided by heavy metal It is for this reason among many others, that continuous treatment with the

arsphenamines to and beyond serological negativity without any interruption by rest intervals now appears as such a vital consideration in the management of early syphilis.

ARSENICAL THERAPEUTIC PRINCIPLES

Methods of Administration.—Arsphenamine has been administered by practically every method except fumigation and inhalation by mouth, per rectum, by subcutaneous injection by intramuscular injection by intravenous injection, intraspinally and intracranially

Of these, administration by mouth was shown by Schamberg and his coworkers to be ineffective though the drug can be given in a capsule with reducing agent such as sodium sulphite Arsphenamine per rectum has been more fully studied Suppositories were for time used in the treatment of infants and persons with inaccessible veins, but in the doses thus employed the drug was practically ineffective and is now completely discarded in favor of the intramuscular use of bismuth and the intramuscular arsphenamine preparations such as sulpharsphenamine and bismarsen. Mehrtens found that five times the intravenous dose (4 Gm.) of neoarsphenamine could be administered by rectal tube high in the sigmoid with the securing of a concentration of the drug in the blood stream considerably higher than that obtainable by intravenous injection. No effort seems to have been made, however to exploit the method or test its ultimate value

Arsphenamine Subcutaneously and Intramuscularly—Ehrlich in 1910 placed intramuscular injection foremost among the methods of administering arsphenamine ("606") from the standpoint of theoretical effectiveness. The necrosis due to the alkalinity of the suspension and the intrinsic tissue-destroy ing effect of the arsenical drug however put a stop to the effort at practical adoption.

So severe were the destructive effects of earlier injections that Takahashi found from three hundred t four hundred days to be required for the restitution of the tissue t an injection site to the stat of quiescent scar If softening and evacuation occurred, the abscess, while sterile contained large part of the injected drug, which was thus lost in the discharge. At the present day the sites of old intramuscular injections of original "606, often calcified to stony hardness are objects of curiosity to the syphilologist

In spite of this initial setback, there has been consistent effort throughout the arsphenamine era t return to intramuscular methods hich deserve t least theoretical commendation. Craig and Harrison have shown that the effect of the intramuscular use of arsphenamine on the Wassermann reaction is definitely superior to that of intravenous injection. Behn and Stokes felt that much of the superiority of sulpharsphenamine, such as it was, depended upon the use of the intramuscular route. The possibility of securing essentially equivalent therapeutic effects by drugs of relatively lower arsenical content, such as bismuth arsphenamine sulphonate when given t short intervals intramuscularly is certainly suggested by our experience with this drug The question as t whether any of the present-day arsenicals have reached an optimum from the standpoint of their usability in intramuscular procedure is, however serious one and far from answered. The demonstration that technic of administration has good deal to do with making intramuscular use even of severely irritant drug, practicable has been convincingly supplied by the work of Harrison, Whit and Mills of the British Army and of Richard Sutton, Fordyce and Rosen in this country It cannot be forgotten, however that ork of this sort has been carried through under army disciplinary restraints or t the exercise of force of personality and professional prestige which the verage pract tioner and even the majority of clinics can hardly expect to bring t bear Reaction and pain produced by methods of treatment, as must be repeatedly reiterated, are grave bar to the success of modern treatment technics and these objections have been far from met by ny preparation now on the market.

Intravenous Arsphenamine Administration.— As the overwhelmingly popular technic of today this forms the background of practically all the treatment principles discussed in the literature and in this book The rates of absorption

of neoarsphenamine and sulpharsphenamine given intramuscularly however are quite similar to those for the intravenous route so that they are to some extent translatable into common terms The technic of these procedures is fully discussed in Chapter VIII

Intra-arterial arsphenamine therapy has been studied in animals by Kritschewski and Winogradowa (1932)

The Intraspinal Administration of the Arsenicals.—In the first edition of this work, the intraspinal administration of arsphenaminized serum and the discussion of its usefulness occupied approximately twelve pages. The change of syphilological front has relegated the method to a position of relatively *minor importance replaced by tryparsamide* and fever therapy though still useful in certain symptoms and complications of tabes dorsalis especially Kierland and O Leary (1941) however believe this attitude toward intra spinal therapy is unjustifiable. The following brief summary here given will assist those who desire to use this method

From the outset two groups of procedures have developed that of Swift and Ellis, who, in 1912, administered serum of arsphenamine-treated neurosyphilitic patients into the spinal canal with favorable results; and that of Ravaut, who in 1913 reported on the direct injection of dilute neoarsphenamine solution int the spinal canal. Later, drainage of spinal fluid to carry the circulating arsphenamine in the blood through the choroid plexus was carried out by Gilpin and Early and endorsed by Dercum. The procedure of Swift and Ellis modified by Ogilvie who "reinforced" the blood serum introduced into the spinal canal by minute amounts of neoarsphenamine, has survived to the present day Modifications of the Ravaut technic in spite of initial difficulties have been developed and endorsed by Wile and Gennerich. The Swift Ellis method, which is the only one that ill now be discussed in this work, had its inception in the observations of Taege Meirowsky and Hartmann, Plaut, Gibbs and Calthrop, and others to the effect that the serum of syphilitic patients has curative properties. Swift and Ellis at first employed the serum some time after the injection of arsphenamine, but inasmuch as the test became negative on the blood serum within two hours after intravenous injection, they were later led to draw the blood within an hour after injection and to inject the diluted, inactivated serum into the spinal canal the following day Such serum has since been spoken of as auto-arsphenaminized because the patient receives intraspinally only such arsphenamine and arsphenamine colloidal combinations as are in circulation in his own blood stream after intravenous injection. Kolmer has in his use of the method emphasized the importance of the time after injection when the blood is drawn. When it is recalled that 60 per cent of the arsphenamine is fixed outside the blood when the injection is just completed, and that at the end of an hour only 10 per cent remains in the circulation, the importance of this consideration is evident. At best, the amount in 15 to 30 cc. of serum obtained at the end of t enty to forty minutes cannot be large. The addition of amounts such as ⅟₁₀ to ½ mg of neoarsphenamine per dose, as practiced by Ogilvie, was therefore rational procedure On the other hand, it was contended by the opponents of intraspinal therapy that the amount added is *not equal to that which can be found in the fluid after massive intravenous* injection. Swift and Ellis, however ascribed considerable effect to the influence of antibodies in the serum and it has been contended that normal nonarsphenaminized serum does not appear to give these same results. Looking back on the matter in the light of our growing understanding of the mechanism of antisyphilitic treatment, it seems very probable that all the intraspinal procedures, including the use of mercury (Byrnes), are essentially that of protein irritant to increase meningeal permeability Whatever may be the mode of action, there is no question in our minds that the buffering of any added drugs by the serum is an essential safety factor in the procedure and that even under the best conditions and with reasonably large experience and trained staff we have never felt the hazards of the Ravaut and Gennerich methods of direct introduction of the arsphenamines into the spinal fluid t be small enough in American practice to justify their continued use

Mechanical factors play part in intraspinal medication and give evidence from the character of the reactions that maximum therapeutic effect is obtained near the point of entry of the injection. This has led both to the introduction of arsphenaminized serum into the ventricles by Hammond and Sharpe, and Solomon, and its use in intracisternal injection after the technic of Ayer Gennerich ingeniously carried the neoarsphenaminized spinal fluid upward from the site of lumbar puncture by running in below it spinal fluid obtained from second simultaneous punc

ture two vertebrae below the first. There can be no question that such method raises the field of action materially higher toward the base of the brain, and the procedure has merit as part of the treatment of primary optic trophy and basilar conditions for which it can be employed.

It cannot be too vigorously emphasized that adequate technical facilities and personnel, knowledge of the principles of the treatment of syphilis as well as an intraspinal technic, and a large bump of caution are essential to the saf employment of such a procedure as the Swift Ellis or other forms of intraspinal therapy The safety range of the method is small and every detail in technic drug, and medical judgment is vital T one who has seen the increase from ½ to ⅓ mg. reinforcement in the practice of confrère seemingly cause 3 successive cases of saddle anesthesia in patients who had previously without difficulty tolerated series of ½ mg. treatments, the safety factor becomes very impressive. T one who has been ppealed to for emergency advice in aid of patient dying of arsenical myelitis after a practitioner had forcibly with syringe, injected fully 2 or 3 cc. of concentrated solution of neoarsphenamine into the spinal canal, the dangers of popularization of difficult technical procedure become pparent. Such small matters, even with the technic t its best, as drop in speed of the centrifuge, by failing to throw out all the red blood cells, may on single occasion make all the difference between crop of reactions and an uneventful day There is no doubt that the general practitioner should not attempt intraspinal measures. Those specialists who are equipped to do so should be exceedingly chary of tentative and experimental variations on the established technic.

With due regard to the physical status of the patient and his tolerance of the arsenicals, Klerland and O'Leary (1941) feel that intraspinal (Swift Ellis) therapy is indicated in patients with asymptomatic and meningeal neurosyphilis early tabes dorsalis, and early neurosyphilis not responsive to a trial of routine treatment. It is of value as postmalarial therapy in neurosyphilis without mental changes, and in certain cases of syphilitic cardiovascular disease with complicating neurosyphilis Moore and his associates have considered intraspinal therapy as second best for optic atrophy

Progress in the Technic of Arsphenamine Administration.—Certain basic essentials involving the solvent, the asepsis, the rate of administration and in the case of arsphenamine 606" itself the technic of neutralization have gradually come to the front as *sine qua non* to an adequate intravenous technic.

Reactions Due to Water—The earlier intravenous injections were followed by reactions, usually febrile in character which, according to the national persuasion of the observer were attributed to the solvent by the Germans and to the drug by the French.

The introduction of commercial methods of issuing solvent with drug in the form of properly prepared ampuled water has now so simplified the situation for the users of neoarsphenamine and mapharsen and the intramuscular modifications that to all intents and purposes only the user of "606" meets the problem in its original significance and proportion.

The Tubing Reaction.—Gum rubber tubing used in the gravity method of administering arsphenamine may contain toxic substances of unknown composition apparently associated with an excess of sulphur compound in connection with the vulcanizing process, as show by analyses performed through the courtesy of the B F Goodrich Co. after Busman and Stokes had published their observations on the reaction The toxic substance is dissolved from the bore of the tube by slightly alkaline solutions and can ultimately be sufficiently dissolved way so that used tubing causes after time to give rise to reactions. The reactions thus come in crops and are severe enough to be thoroughly alarming and t times even conceivably f tal They are described in connection with the prevention of reaction in Chapter IX. Typical toxic responses can be produced in dogs by the use of new rubber tubing of toxic brand in the adm nistration of dilut sodium hydroxide solution intravenously or even of citrated blood. The reaction can be entirely prevented, as indicated in the *Public Health Service technic, by soaking all rubber tubing over night in normal sodium hydroxide solution*, being careful that all parts of the lumen of the tube are reached.

Concentrated Solutions of th Arsphenamines.—Undoubtedly large part of the striking lead held by neoarsphenamine over the original "606" is to be attributed t simplification of

the technic of intravenous injection of the former drug which as reported by Ravaut in 1912. He showed that neoarsphenamine could be administered without injurious effects in concentration of 1 cc. of properly prepared distilled water per decigram. This concentration permitted the use of the syringe in place of the more cumbersome gravity apparatus, did away with the increased possibility of reaction incident on the injection of large amounts of hypotonic solution and perhaps improperl prepared solvent, and permitted the use of small needles with less discomfort to the patient and less damage to the vein. An enormous saving of time was at first realized by rapid injection, double-edged advantage, as was later discovered when the time factor in reactions began to be ppreciated.

The concentration of sulpharsphenamine and bismuth arsphenamine sulphonate for intramuscular injection is substantially higher than for intravenous use and 1 to 2 cc. of solvent represents the maximum amount advised In fact, the higher concentrations seem to be better tolerated than the lower ones.

Acid Arsphenamine (606) Solution.—Efforts t produce vest pocket technic for the administration of original arsphenamine (606) have not been so successful. Neutralization and dilution, with gravity administration is thus far absolutely unescapable with this drug. All efforts to do way with the neutralization of arsphenamine, with or without the original dilution requirements (40 t 50 cc. solvent per decigram) can be regarded now as obsolete Schamberg, Raiziss and Kolmer showed acid arsphenamine solution t be 50 or 60 per cent more toxic than the alkaline disodium salt. The concentration of alkaline arsphenamine solutions has likewise been attempted and in place of the original Ehrlich specifications of 50 cc. per decigram and the present Public Health standard of 25 cc. per decigram, arsphenamine (606) was given by Brayton and Nelken in concentrations of 10 to 20 cc. of solvent for the entire 4 and 6 dg. doses. Cannon (1920) revival of the syringe technic for arsphenamine injection has not thus far been widely used. W have had personal experience with all modifications of this type of procedure, using water as solvent, and can unhesitatingly condemn it as giving rise t disconcerting proportion of reactions on the table, prostration, vomiting, pain in the back, sweating and weakness, even if no pneumonias ensue Injury to veins is common. It is possible that thorough study of buffers, including gelatin, might yield results that would lead to the popularization of concentrated solution technic for "606.

Use of Buffers and Chemically Modified Solvents.—A number of efforts have been made to modify the toxicity of the arsphenamines by the use of special vehicles, including blood serum, glucose solution, gelatin solutions, calcium chloride, sodium cosinate, sodium thiosulphate vitamin C and its derivatives. Physiologic salt solution is, of course, the simplest modification of solvent possible and where quantities larger than 100 cc. are to be given there is apparently some reduction in toxicity probably due to the influence on hemolytic effect and on the irritation of veins leading to spasm and thrombophlebitis.

Adrenalin can also be added t arsphenamine solutions though for its physiologic effect rather than for any chemical modification of the diluent This plan, tried at the Mayo Clinic, by Osborne (unpublished) proved helpful and deserves further study It occasionally makes possible the treatment of patients who would be otherwise obliged to discontinue treatment because of nitritoid reactions but is only recommended in the case of the larger dilutions employed with arsphenamine.

The Rate of Administration.—This implies the rate of delivery of the drug to the blood stream rather than the rate of injection of solutions of varying concentration and in today practice is reducible to a simple rule of thumb — deliver arsphenamine solutions slowly and mapharsen fast. By Public Health Service standards, arsphenamine should be delivered at the rate of one decigram per minute (20 cc. of solution) and one decigram in thirty seconds for neoarsphenamine A reactionless office technic calls for even slower administration in markedly reactive patients, and it is only w th the greatest difficulty and the most determined attention to the matter that one can keep his tendency to speed up administration down to the limits of greatest safety The adoption of automatic controls, including needles so small when used with

a syringe technic that it is impossible to give a hurried injection, and burette clamps on the tubing of gravity apparatus are desirable Mapharsen in contrast to the arsphenamines should be so injected in the words of the manufacturers, that the time elapsing from the insertion of the needle until the syringe has been emptied and the needle removed from the vein should be no more than thirty seconds " The official five-day intravenous drip technic calls for an hourly dose of mapharsen of 0 02 Gm. in 200 cc. of 5 per cent dextrose solution The daily dose is 12 hourly doses or 0.24 Gm carried in 2000 to 2400 cc. of dextrose solution Leifer gives the rate as 3 cc. per minute

Temperature of Solvent.—Practically all drugs of the arsphenamine group are now dissolved in water at room temperature.

Local Anesthesia—Efforts have been made to overcome the discomforts of intramuscular injection of the arsphenamines by the use of local anesthetics, as in the case of bism th preparations. Two per cent novocain or butyn, tw t four drops in the solvent, may be employed and seem helpful

Dosage and Interval in Arsphenamine Administration.—*Before taking up* this topic it would perhaps be well to refer to Fig 100 which gives some dosage maxims applicable in general to syphilotherapy The effects, both therapeutic and toxic, produced by the arsphenamines are functions of a rather complex dosage technic which must be mastered if the best results are to be obtained The factors of greatest practical importance are discussed below

Arsenical *vs.* Therapeutic Equivalents.—The proper determination of the dose should be if possible on the basis of therapeutic effect as determined by the trypanocidal index. Using this method of determination Kolmer made the important observation that the therapeutically equivalent dose of neoarsphenamine as compared with arsphenamine is not one third greater but twice as great. Thus, if 0 6 Gm is the maximum therapeutic dose of arsphenamine 1.2 Gm will be the maximum therapeutic dose of neoarsphenamine one of course comes into collision with toxicity and in certain cases the conflict will be irreconcilable so that it will never be possible to secure the same therapeutic effect from one drug that can be secured from another On the other hand, it is possible by adjustment of intervals between injections to compensate to some extent for the effect of reduced dosage and in this simple statement lies the secret of much disappointment in the use of the less powerful arsenicals on dosage systems which, with respect to interval particularly are adapted only to the most powerful Thus, the interrelations between dose and interval have led to the development of what might be called "course" concepts in arsphenamine technic.

The Arsphenamine Course—Course concepts in the use of the arsphenamines unfortunately rest on a less satisfactory biochemical basis than do those outlined in Chapter VI for bismuth Part of this state of affairs depends on the greater difficulty of interpreting the metabolism storage and toxicity of arsenic as compared with bismuth. The results of intensive therapy which are still in process of evaluation, may entirely change our concept of courses and dosage of arsenic per kilogram necessary to produce "cure" (see Chapter V)

The Shift Toward Continuity of Administration.—Recent years have brought a definite shift toward continuity of treatment in the use of the arsenicals administered by standard treatment systems. It has become apparent that the safety margin of the drugs with properly adjusted dosage is large that

reactions are, to a considerable extent, due to technical error and misapplication that the close observance of every prescribed precaution makes possible the very great prolongation of treatment in time and that moderation in dosage still further increases tolerance without serious loss of therapeutic

Fig 100

A SUMMARY OF ARSENICAL THERAPEUTIC PRINCIPLES

1. Know the system applicable to the selected drug; never expect the best from one drug by the system adapted to another
2. Know the arsenical content and attempt to secure therapeutic equivalence by frequent smaller or less frequent larger doses.
3. Know the complications, administration technic and after-care peculiar to each drug. Here lies our worst weakness. Many complications are avoidable and preventable.
4. Treat *continuously not intermittently or irregularly in early syphilis.*
5. Treat intermittently or with alternations and rests in late syphilis.
6. For "606" use the weekly interval and 6 to 12 injection course
   For neoarsphenamine use three to five days early one week late and 10 injection courses.
   For sulpharsphenamine use one week and 8 to 10 injection courses.
   For mapharsen use three to five days in early syphilis, weekly in late syphilis, 10 injection courses. Foreshortened intensive systems described in Chapter XIV
   For bismuth arsphenamine sulphonate use three to seven days and 30 to 60 injection courses.
   For silver arsphenamine use five to seven days and 8 to 12 injection courses.
7. Dosage for women (unless pregnant) now tends to equal that for men, weight for weight.
8. Initial dosage is never more than half full dosage.
9. In arsphenamine "preparatory treatment" for avoiding therapeutic shock and paradox, initial dosage is nearer one tenth adult normal, very slowly increased
10. In early syphilis, less than half the adult full dose is subtherapeutic and favors relapse and failures.
11. In relying on an arsphenamine alone, give adult male 0 07 to 0.1 Gm. per 25 pounds body weight with "606" 0 1 to 0.15 Gm. with "914"; 0.01 Gm. with mapharsen; 0.05 to 0.07 Gm. with silver arsphenamine; 0.05 to 0 07 Gm. with sulpharsphenamine; 0.05 Gm. twice as often, with bismarsen. The curative total dose of mapharsen is currently rated at 1200–1800 mg (20–30 mg per kilo)
12. In giving heavy metal simultaneously reduce the maximum dosage given above one third, the minimum dose not at all.
13. Never begin with an arsphenamine on the above dosage scales if the patient
    (a) Is incompletely examined.
    (b) *Shows signs of serious localization of syphilis to vital structures, especially heart, liver nervous system, eye, or ear*
    (c) Is a "wreck" from other cause.
    (d) Is an untreated diabetic
    (e) Has active tuberculosis.
    (f) Is sharply febrile
    (g) Has an extensive unexplained dermatitis.
    (h) Is a high-grade nephritic
    (i) Has had trouble with the drug before
    (j) Is in danger of neurorecurrence (see early syphilis)
14. A system of treatment ending with an arsphenamine is left hanging in the air Bring it safely down to ground with a heavy metal tail.
15. Don't blame "idiosyncrasy" and reactivity automatically on drug or patient, and stop. If the situation is beyond you, seek advice without delay

effect. Probably the crucial demonstration was that of Moore and Kemp, and most recently of the American Cooperative Group, on the paramount worth of continuity as a general principle in the treatment of early syphilis This however cannot be literally applied to the use of the arsphenamines, which

were, in fact, employed intermittently in the systems of treatment involved in the work of these investigators. In a sense, continuity of treatment effect reaches its peak in the single massive dose systems now coming into use (see Chapter XIV)

Some astonishing records of tolerance, particularly for neoarsphenamine exist, several patients with neurosyphilis in our experience having received from their practitioners a hundred or more weekly injections without a break; and one report by Photinos apparently establishes a world record—that of a woman with prenatal syphilis who weighed only 39 to 45 Kg. (85 to 100 pounds) yet who tolerated without the slightest sign of reaction 230 injections of neoarsphenamine in an elapsed time of approximately three hundred and sixty weeks (1922 to 1929) 190 injections of the series being of the maximum dose of 0.9 Gm.

Whatever may be said of the merits of continuous treatment in early syphilis, the intermittent use of the arsphenamines is still distinctly the preferred technic for late syphilis, where resistance-building is often more important than direct action on *Spirochaeta pallida*

The Interval between Arsphenamine Courses.—In early syphilis this is determined in the continuous system of treatment by the heavy metal where it is used in alternation with the arsphenamines, or by a piece of empirical guesswork as to the rate at which accumulated arsenic from a prolonged course is likely to be eliminated. In general it may be said that intervals longer than six to eight weeks between courses of "606" even though filled by a heavy metal, represent the upper limit, and four weeks the lower limit in vigorous treatment, especially of early syphilis In the treatment of latent and late infections these intervals between arsphenamine courses are prolonged to ten or twelve weeks while the heavy metal is being administered, and may even be added to by an additional complete rest period from all treatment ranging from four to six weeks In general, the principle which should apply is essentially that of individualization and evaluation of the acuteness of the process A bonfire in the nervous system, if it is not at once subjected to tryparsamide or fever therapy should be subjected to prolonged continuous treatment as in an early infection. A relatively stationary process in a greatly debilitated individual demands periods of recovery from the therapeutic pounding for full utilization of the tonic effects of arsenical drugs.

Certain Tolerance Concepts.—Just as it is becoming evident that the arsphenamines may be used in longer courses than was at first believed advisable, so it has been shown though to what good purpose it is difficult to say that enormous doses of these drugs can be tolerated without serious degrees of reaction, provided the technic of administration is irreproachable.

Initial Dose, Age Weight and Sex Factors.—The principles governing *initial dosage* are summarized under items 7 8 and 11 of Fig 100 and are absolutely dependent on the absence of discoverable contraindications At no point in the treatment of syphilis at the present day could the profession better afford to sloganize individualization, for the damage done by the first injection of an arsphenamine is often serious and too often irreparable. Initial dosage should always be modified by a consideration of the patient's general condition, the special structures involved and the activity of the syphilitic process. Between the pitfall of subtherapeutic dosage and the dangers of therapeutic shock and paradox, the half-dose rule constitutes only a fair compromise and should not be routinely applied beyond the secondary stage of the disease or the period of latency

Weight factors, while the most obvious of all to the laboratory worker are often the hardest for the clinician to grasp One sees otherwise competent men administering identical doses to strapping policemen and scrawny girl clerks without a moment s reflection, evidently slaves to a dosage table While in the middle range of adult weights, 140 to 160 pounds the ordinary adult maximums apply for the effect which one desires to produce a weight-dosage ratio for each of the commonly used drugs in American practice is given under item 11 in Fig 100 Arsphenamine dosage for women formerly accepted at two thirds to three fourths that of men is now more and more nearly identical weight for weight. In old age it is more important to make a physical appraisal and be guided by the conditions found than by mere age. The dosage for early syphilis in elderly robust men may be reduced one fifth below that for the young adult. In infancy the dosage is usually given by age, but above 100 pounds weight an adult scale may be employed for neoarsphenamine or sulpharsphenamine, the dosage scale up to three years being

	Intramuscular Gm	Intravenous (jugular) Gm
Under two weeks.	0.05	0.03
Two to twelve weeks	0.1	0.03–0.1
Three to nine months.	0.15	0 1 –0.15
One to two years.	0.2	0.15–0.2
T to three years	0 25–0.3	0.2 –0 3

From three to eight years of age the dosage reaches 0.5 Gm. neoarsphenamine intravenously for therapeutic equivalence from eight to twelve years it is 0 6 Gm The initial intravenous dosage up to three years should not exceed 0 05 The dose of "606" at twelve years is 0.3 Gm that of bismuth arsphenamine sulphonate is 3.5 mg per pound or 7 mg per kilogram of body weight. A practical schedule based on age as employed by Chambers and Koetter is given in Fig 101 For children the initial dose of arsenoxide (mapharsen)

Fig 101

DOSAGE OF BISMARSEN IN CHILDHOOD

Age.	Dosage (dissolved in 2 cc. solvent)	
Tw weeks	10 t 20 mg	0.1 to 0.2 cc.
Two to six eeks	20 to 30 mg	0.2 to 0.3 cc
Six to twelve weeks	40 to 50 mg.	0.4 t 0.5 cc
Three to twelve months	75 mg.	0.75 cc.
	Dissolved in 1 cc. solvent	
One to tw years	100 mg	0.5 cc.
Two to three years	100 mg	0.5 cc.
Three to four years	100 t 150 mg	0.5 to 0.75 cc.
Four to five years	150 to 200 mg	0.75 to 1 cc
Five to fourteen years	200 mg	1 cc

From Chambers and Koetter Arch. Dermat. and Syph., 23 1065, 1932

should not exceed 0.0005 Gm (0.5 mg.) per kilogram of body weight the tota dose should average between 0 0005 and 0 001 Gm (between 0.5 and 1 mg) per kilogram of body weight.

Pregnancy demands, in our experience systematic reduction of dosage to about two thirds the adult normal by weight, to insure safety In febrile

conditions of nonsyphilitic origin it is wise not to exceed 0.1 Gm. neoarsphenamine for the first dose to test the tolerance. In diabetes and anemias, particularly of the primary type, the dosage for the first several injections should be one half to two thirds normal weight scale and if acidosis is present, the diabetic phase should be treated before arsphenamine is begun. Lesions of the second and eighth cranial nerve, early or late, call for great caution in dosage at the outset and preparatory treatment with a heavy metal is preferable. To avoid therapeutic paradox, if an arsphenamine system is selected, very slow increments of dosage, beginning with 25 mg. of neoarsphenamine or bismuth arsphenamine sulphonate at intervals of two to four days is the only safe approach.

Dosage and Interval in Nonspecific or Resistance-building Effects from Arsenical Treatment.—One half or two thirds the maximum dosage with weekly intervals and series of eight to ten injections the interval being extended toward the last and an interval of two to four months between arsphenamine courses is appropriate to the securing of this type of effect, discussed in greater detail on page 150.

THE TRIVALENT ARSENICALS INDIVIDUALLY

Comparisons of the Arsphenamines and Selection of Drug for Various Purposes.—While the practitioner is inclined to take a little too seriously the pharmaceutical fireworks that accompany on to the market each slight shift in the molecular formula, there is, especially in the last several years a distinct trend toward significant improvement in the trivalent arsenicals. It is unwise, however to expect radical and startling differences with each new modification, when at best the variation introduced may not affect 10 per cent of the patients on whom it is used in any distinctive fashion.

Estimation of the Value of an Arsphenamine.—The evaluation of the clinical worth of an arsphenamine is somewhat less difficult than that of heavy metal, but none the less is by no means easy. It cannot be accomplished by any one criterion. It is very apparent from the clinical course of syphilis in general that reversal of the serologic reaction as such does not appraise the ultimat influence of the drug upon the infection, for many infections retain full virulence and even infectivity and go on to disastrous complications under cover of negative blood serologic reaction. The healing of lesions is not holly trustworthy. The disappearance of spirochetes from lesions within varying periods of time is not proof of the ultimat curative power of the drug under investigation. Observation for relapse is too seldom part of clinical reports. The superiority of new preparation can be demonstrated to some extent by employing it upon cases in which the older preparations have failed. The fact that the new preparation may succeed because it offers another angle of attack on drug-fast organism and that it may be no more effective as routine treatment of many cases than the drug it supplants, must, of course, be borne in mind. The usefulness of an arsphenamine is dependent not alone upon its action on the disease but upon its reaction on the patient. Increased mortality and increased incidence of serious if not fatal complications, such as dermatitis, may make the use of even powerfully curative drug inadvisable. A notable example of this, in our opinion, is comparative newcomer the therapeutically effective sulpharsphenamine. On the other hand, systematic detoxification, as we have several times remarked, may be carried through t the expense of therapeutic effectiveness. Preparations which have been in clinical use for only three or four years cannot be regarded as completely out of the experimental stage and should be employed with the greatest circumspection by the inexperienced or the practicing profession t large. The therapeutic guides given are only tentative and may be reversed within comparatively short time by improvements in manufacture and technical administration as well as fuller study of clinical effects.

Arsphenamine Proper (606) from the Therapeutic Standpoint.—The onrushing revolution of massive dose and intensified systems with and without

fever therapy will, almost inevitably remove from the field of practice the landmark of arsphenamine "606" the basis of all comparison in the past twenty years the most widely used drug in the Cooperative Clinical Group the pet of specialists, and the one which most syphilologists familiar with the older systems would select, if they could for the treatment of their own infections were they so unfortunate as to acquire them. Accordingly all extended discussion of this drug in theory is here omitted and reference should be had to the *second edition of this work.*

Neoarsphenamine.—The enormous popularity of neoarsphenamine was due to ease of administration combined with a comparative freedom from immediate and disconcerting complications It is now rated as the most reaction-producing of the standard and generally used trivalent arsenicals, sulpharsphenamine perhaps excepted. It is much more variable than "606" with regard to therapeutic effectiveness and it has been clearly shown both by Dale and White and by Voegtlin and his associates that individual lots of the drug on the open market may be absolutely worthless therapeutically even though they may have passed the official toxicity tests and be to all appearances perfectly satisfactory *Much of this lack of uniformity has now been ironed out* (Probey 1939) Dale showed the relation of toxicity to solubility the more soluble being the less toxic drug

Raiziss, Elvove Freedman and others have shown that what is marketed as neoarsphenamine often contains sulpharsphenamine-like bodies in relatively high proportion and it appears from the work of these various investigators that there are at least two and possibly three quite distinct types of neoarsphenamine on the market. Similar observations were made by Fordyce Rosen and Myers and connected with the erratic reactivity of the drug as employed therapeutically The toxicity of neoarsphenamine, dose for dose, is 2.5 times less than that of arsphenamine (Raiziss) and its solutions are nonhemolytic (Kolmer and Yagle)

The basic disadvantages of the drug, which must be taken into account in routine therapeutic work, include its rapid oxidation and the enormous increase in toxicity which takes place on shaking or other forms of aeration of the solution. This increase may amount to a hundred times within a few moments, as Roth has shown. The reaction expectancy of neoarsphenamine increases with the age of the drug (Probey and Harrison, 1938) In addition these investigators (1939) reported that temperature, time of exposure and *moisture content of the powder affect the stability of neoarsphenamine the* deterioration varying directly with these factors. The drug must therefore be made up dose by dose, and handled with genuine delicacy and attention to detail. It is the mark of the greenhorn to squirt neoarsphenamine solutions, for example, from syringe to tumbler Once in a syringe free from air bubbles however its toxicity does not increase for several hours, as Kolmer Schamberg and Brown have shown. Much of the technical detail, quite as significant though less vexatious in time consumption than that involved in the use of "606" has not been appreciated by the average physician. In contrast to arsphenamine, neoarsphenamine should never be allowed to stand. If it does not dissolve almost instantly it should be thrown away and complaint made to the manufacturer In its therapeutic use, smaller doses, shorter intervals, and longer courses should be the rule and the once-a week standard of "606" administration laid aside. The drug lends itself particularly well to combined use with bismuth to the securing of tonic effects in debilitated patients and nonspecific effects on patients who do not have syphilis (p 151) In the latter case the longer intervals are however employed. Although 0.3 Gm. is accepted

as an initial dose for the average adult, it is on the borderline of questionable effectiveness especially in early syphilis, and should be promptly increased with the second or third injection. The distinct tendency to erratic behavior in neoarsphenamine makes it wiser to use smaller doses and shorter intervals than to risk the maximum doses of 0.9 Gm even with weekly intervals

Comparisons of Arsphenamine and Neoarsphenamine: Therapeutic Effectiveness.—Cannon and Karelitz, studying the action of the two drugs in infections of not more than six months duration when treatment was begun, with subsequent treatment and observation periods of not less than six months, found in 430 patients that arsphenamine was clinically the more effective drug As criteria they used the disappearance of visible lesions; the reversal of the Wassermann reaction complications arising from administration of the different drugs, and the number and nature of relapses. Heavy-metal treatment was in many cases used concurrently

The Cooperative Clinical Group found in its material dealing with this question, involving comparison of 2534 cases treated with arsphenamine (606) and 355 cases treated with neoarsphenamine (914) under the same conditions, that "606" in its various combinations with heavy metal therapy reverses the blood Wassermann reaction to negative within three months or less in 28.5 per cent as against 18.9 per cent under neoarsphenamine. This efficiency is approximately one and five-tenths times that of "914 One and one-half times as many fixed positive blood Wassermann reactions resulted from the use of neoarsphenamine alone or in combination as from arsphenamine (606) When systems of treatment (continuous, intermittent, irregular) were compared, "606" maintained its efficiency ratio of better than one and one half as compared with neoarsphenamine (35.9 per cent *versus* 20.5 per cent) ultimate good results under continuous treatment. Under intermittent treatment the lead of "606" was somewhat less pronounced and in irregular treatment there seemed to be relatively little choice The category of ultimate results included cured with examination, cured without reexamination, patients placed on probation, relapse or resistant serology and reinfection.

Undoubted consolation for the comparative showing made by neoarsphenamine was obtained from the Cooperative Clinical Investigation, which showed that the two drugs approached equality when used with the heavy metals 13.6 per cent of "606" reversals to negative in the first three months, as compared with 10.9 per cent "914 reversals; and 33 4 per cent reversals *versus* 35.7 per cent for the same combinations in four to twelve months. Thus, though neoarsphenamine is slow in securing reversal at the outset it catches up with arsphenamine when used in combination with heavy metal No superiority is apparent on the part of the bismuth combinations as compared with the mercury combinations. Neoarsphenamine, although it catches up with arsphenamine in the serologically reversible case, loses ground seriously in the long run in its failure to prevent fixed positive Wassermann reactions and Wassermann-fastness. This same question may ultimately have to be raised for the arsenoxides Reaction comparisons between the two drugs carried out by Cannon and Karelitz, by the Cooperative Clinical Group, and by Cole's examination of Western Reserve University clinic material, has tended to indicate that arsphenamine "606, originally considered much the more toxic as compared to neoarsphenamine is in reality perhaps under modern methods of manufacture, a very close second, and even from the standpoint of late serious reactions, superior to neoarsphenamine The figures are summarized in the text of the second edition.

Mapharsen.—Ehrlich discovered arsenoxide comparatively early in his studies but he and his associates (1910) felt that while arsenoxide was highly spirocheticidal it was too toxic for clinical use. This view was strengthened by Voegtlin and his coworkers (1923) who found that the increased toxicity of the arsphenamines on standing was due to arsenoxide. Rosenthal and Probey (1933) also showed that the toxicity of the compound was ten times that of arsphenamine Interest in this preparation was reawakened by Tatum and Cooper (1934) who found that in experimental syphilis its chemotherapeutic index was high. These findings were confirmed by Gruhzit (1934–35) but not by Raiziss and Severac (1935) By a reduced dosage schedule the drug was then introduced into clinical practice

The revival of arsenoxide (mapharsen) by Tatum and its application to the general therapy of syphilis by his clinical associates Lorenz and Foerster

(1935 1937) and also in mass study by Gruhzit and Dixon (1938) is probably the most important single contribution to the arsenotherapy of syphilis since the introduction of neoarsphenamine. Judged by the short-term elements in the standards of evaluation Stokes and Beerman (1941) state that arsenoxide (mapharsen) *has met every requirement. It is rapidly spirillicidal and convincingly* effective in the healing of lesions, reduction of serologic tests to negative, and other forms of symptomatic response. For the length of time it has been in use it has an excellent record in the prevention and control of *asymptomatic* neurosyphilis The bibliography of the drug is as yet deficient in thoroughgoing study of infectious relapse In late syphilis of special systems it is at least as effective as the arsphenamines in late syphilis of the nervous system, no more and no less effective Its worth in pregnancy is probably though not as yet demonstrably that of the arsphenamines though Castallo, Coppolino, Rakoff Roeder and Dickson (1939) in a group of 110 pregnant women, treated with mapharsen and bismuth rated the drug definitely less effective than neoarsphenamine in the treatment of syphilis in pregnancy because it does not afford as good protection to the fetus during the period of treatment, and complications in the mother especially gastrointestinal, are more frequent than they should be. Morgan (1938) treating congenital syphilis, rates it more effective in reversing serologic tests than any other arsenical compound previously used. Cornell and Astrachan (1938) gave the drug intramuscularly and refused to draw conclusions as to its effectiveness on account of the low dosage employed. Howles (1939) found this drug good in his experience in treating 204 congenital syphilitics. Chargin and Leifer (1938) treated 50 consecutive Wassermann-fast patients with mapharsen, to find that the drug is neither more nor less effective than any other arsenical in the management of this type of patient. Cole and Palmer (1937) in a careful study of 242 patients of whom 185 were in the primary or active secondary stage, employing a total of more than 5000 injections, apparently rate the drug as approximately *the equal of the more familiar arsphenamines. There is a notable* absence in the literature of comparative series run in similar conditions in the same clinics, using mapharsen parallel with the older arsenicals.

One of the strongest talking points" for mapharsen is the undoubtedly greatly reduced incidence of reaction to this drug Nitritoid crises, often a serious annoyance with the older arsenicals, is all but absent with mapharsen. Epstein (1941) compiling data from 92,000 mapharsen injections, found skin reactions, including exfoliative dermatitis, from one-half to one-third or even one-ninth as frequent as with the standard arsenicals. This is especially true of exfoliative dermatitis. Rein and Wise (1939) listed nineteen types of reaction recorded to 1939 including practically everything made familiar by the older arsenicals except aplastic anemia, of which at the time of their writing there was not a single recorded case but which has been subsequently reported (Kirkham and Perlmutter 1941) They report one death, but fatal accidents are certainly extremely few One of the strongest tributes to the low toxicity of arsenoxide is the experience of the Hyman Chargin, Leifer group and many others working with massive arsenotherapy in which substitution of mapharsen in total dosage as high as 1200 *mg* has not served to approach the toxicity of neoarsphenamine in an average dosage of 4 Gm. (4000 mg.) On the staying power of mapharsen very little is as yet of necessity available. Colonel Harrison (personal communication) has expressed the opinion that the most serious deficiency of mapharsen will be in the direction of permanence of

results (see Chapter V) Taking into consideration all the various factors entering into the efficiency of an arsenical it seems reasonable to expect that as in the case of neoarsphenamine any existing intrinsic deficiencies will be taken up in the modern systems of treatment by the use of bismuth as a heavy metal bringing the level of effectiveness of combined mapharsen-bismuth therapy fully up to the standards achieved by the conventional arsphenamine and neoarsphenamine therapy by a combined continuous (CCG) therapeutic systems

Always more or less parenthetically but nonetheless usefully it should be pointed out that mapharsen is a valuable substitute for other arsenicals when these have proved reaction-producing in the individual case Reports on this matter include those of Jordon and Traenkle (1937) Goldberg (1939) Schoch (1940) Epstein and Falconer (1940) Falconer and Epstein (1940)

Sulpharsphenamine —This drug exhibits the curious paradox of warm allegiance on the part of some undoubtedly competent observers side by side with damnation from others equally competent. Stokes and Behn pointed out the phenomenally high incidence of hematopoietic and dermatitic accidents with the high therapeutic effectiveness predicted by Voegtlin Relatively non reaction-producing and therapeutically effective when given to children, it has been subjected to so much criticism on the score of grave reaction produced in adults that its status was reviewed by the Council on Pharmacy and Chemistry in 1932 and the *pros* and *cons* there discussed. The late Dr Albert Pfeiffer (1935) who strongly supported its continued general use by the New York State Department of Health compared the reaction incidence in 29,510 in ections with the statistics of the Cooperative Clinical Group insisting that sulpharsphenamine s record was fully equal to that of the other arsphenamines. He stated that in the New York State Clinics, there were no cases of aplastic anemia, cerebral hemorrhage acute yellow atrophy or ocular damage and no deaths from the drug. Osborne Rickloff and Butler (1933) in parallel tables showed that the incidence of jaundice was 1 in 800 injections for arsphenamine (606) for sulpharsphenamine 1 in 179 injections Dermatitis occurred in 1 of 850 injections following arsphenamine whereas it occurred in 1 of 298 injections following sulpharsphenamine. There were no cases of purpura following arsphenamine whereas two followed sulpharsphenamine. The United States Navy Medical Department (1940) using sulpharsphenamine from 1925 to 1939 among 20 438 injections, reported 17 mild 8 severe and no fatal reactions to sulpharsphenamine During the year 1939 943 doses of this drug were administered with no reactions whatsoever In the fifteen year period the incidence of reactions of 1 to 1178 doses of sulpharsphenamine is somewhat higher than the average ratio of 1 to 1470 doses of 8 arsenicals trivalent and pentavalent. In general it is clear therefore that the weight of opinion is opposed to the use of this drug in adults, but sanctions its use in the treatment of children

Bismuth Arsphenamine Sulphonate (Bismarsen—Bismuth Sulpharsphenamine) —This drug synthesized by Raiziss in 1925 contains 12 to 15 per cent of arsenic and 23 to 25 per cent of bismuth It should never be given intravenously and when given intramuscularly is dissolved in 1½ cc. of distilled water containing a local anesthetic *The combination is a rational one and* Kolmer has found that the trypanocidal activity is greater than that of "606" in equivalent doses of arsenic, thus supporting the contention of Lehnhoff Wyld that the activity of an arsenobenzol compound is increased by the

presence in the circulation of another metal. It is important to emphasize the fact that the drug can and should be used continuously for long series if its best qualities are to be brought out, and that the interval between injections where maximum effect is desired should not be greater than three or four days. When these requirements are overlooked or disregarded relatively unsatisfactory results are sure to follow. The series of injections in the more recent work of this drug frequently number 60, 80 or even 100 in length and should not be broken up into courses or interrupted by other methods of treatment.

The advantages of the drug include: (1) Exclusively intramuscular administration with comparatively little local reaction and measurable therapeutic effect, in many cases, with injections only once a week (though in early syphilis 2 injections a week are desirable); (2) susceptibility of administration in long courses; (3) very low incidence of complications attributable either to arsphenamine or bismuth, which makes the drug a valuable substitute for the other arsphenamines that may have set up reaction in a given case; (4) a very high proportion of lasting good effects on the blood Wassermann reactions; (5) low incidence of neurosyphilis when the technical precautions above described are strictly observed in early cases; (6) absence of therapeutic shock and paradox in cardiovascular and hepatic syphilis, provided the initial dosage is very small (0.05 Gm.) and (7) ease and simplicity of preparation for administration.

The disadvantages include (1) a slower spirillicidal effect than that of neoarsphenamine, though more rapid than that of some bismuth preparations. This delay is sufficient to justify beginning treatment in early syphilis with a more rapid spirillicide such as arsphenamine, for the first 1 or 2 injections. (2) The drug is not absolutely free from complications and shows possibly somewhat more tendency than neoarsphenamine to give rise to aleukemia hemorrhagica. Jaundice and dermatitis are however very rare complications of treatment with this drug. (3) Local reaction after injection is sufficient in some cases (8.2 per cent) to compel a change to another drug. The drug is fairly effective against symptomatic late syphilis but (4) practically ineffective against the serological changes; and hence cannot be particularly recommended for use in this field. In prenatal syphilis the results are still under discussion but have not thus far been striking in the older latent cases. In latent Wassermann-fast acquired cases, bismuth arsphenamine sulphonate presents no intrinsic advantages not obtainable by varying the mode of treatment with other combinations. It may be said, however, that the drug, in combining both the arsphenamine and the bismuth phase of treatment, accomplishes in one motion what ordinarily requires two, with less risk of complications and better general tolerance of a prolonged though moderate treatment regimen.

The original paper by Stokes and Chambers, reporting two years' experience with the drug, has been followed by other studies, some condemnatory (O'Leary and Brunsting), and others commendatory of its use in certain phases of the disease. Kolmer, who more nearly approached our methods in the treatment of early syphilis than did O'Leary and Brunsting, obtained, on the whole, very good results. Tobias, and Haddon and Wilson have found it very useful in tabes for the relief of pain especially. W (Stokes, Miller and Beerman, after five years) were particularly impressed with its usefulness in cardiovascular syphilis and when it is possible to give it with sufficient intensity the results in early syphilis, in our opinion, compare very favorably with those obtained by the older drugs. Our early confidence in this drug has been reaffirmed by a review of fourteen years' experience (Beerman, Shaffer and Livingood, 1942). Haddon and Wilson rated the drug as superior to tryparsamide except for tonic effects in the treatment of tabes. De Shivers had excellent results in early syphilitic meningitis. Rabies and Severac reported on its efficiency in experimental syphilis.

Silver Arsphenamine and Neosilverarsphenamine.—These drugs, put forward by Kolle during the first World War, have slowly achieved a recognized place in syphilotherapy, although the first burst of publication has not been followed up by much elaborate or detailed study. Silver arsphenamine especially continues to be used with accumulating evidence that it is really from the therapeutic standpoint one of the most effective of the arsphenamines. Cannon (1031), in comparing it with arsphenamine and neoarsphenamine, found serologic tests reversed in a fewer number of injections of silver ars-

phenamine a smaller amount of the drug and a slightly shorter length of time than the neoarsphenamine. Its superiority over neoarsphenamine was apparent also in the healing of lesions and in the achieving of satisfactory end results it stood only very slightly below neoarsphenamine The fear of argyria which has had an important influence on the use of this drug is well grounded Pillsbury and Hill (1939) collected 10 cases of argyria from the use of silver arsphenamine In their summary it stands third among all silver compounds responsible for argyria. While this incidence is not intrinsically high in proportion to the use of the drug the complications are so disconcerting and medicolegally serious as materially to discourage the use of the drug

Spiegel states that it is inadvisable t give more than 8 Gm. of the drug as total treatment if argyria is to be voided. The dosage of silver arsphenamine is for women not in excess of 0.2 Gm. and for men from 0 25 to 0.3 Gm.

Solusalvarsan; Thioarsene; Triosdarsen.—These three trivalent arsenicals have received considerable study in recent years. Solusalvarsan (*Acetyl-glycarseno-benzene*) was found to be relatively ineffective and reaction-producing (Harrison, 1939 Guy Goldmann and associates, 1940)

Thioarsene likewise was rated as unsatisfactory by various investigators (Robinson and Moore (1935) and others)

Triosdarsen (trisodium salt of 3,3' diamino 4 4 dihydroxyarsenobenzene N N d methylene sulfoxl acid) ha had an extended and carefully conducted clinical trial t the hands of the Syphilis Clinic of the University of Pennsylvania (1937 1940) and of Givan and Villa (1939) in the Pediatrics Department of the Long Island College of Medicine, and the Brooklyn Eye and Ear Hospital. The former authors found the reaction incidence compared with several other series, including arsphenamine neoarsphenamine and mapharsen, to compare favorably with and even to be lower with respect to mild reactions than that of most of the named drugs. With respect t severe reactions, there was some tendency t increased frequency of dermatitis and hemorrhagic reaction, as previously observed in most of the sulfarsphenamine group of drugs. The distinctive characteristics of triosdarsen include superiority to neoarsphenamine with regard to the rat of healing of primary and secondary lesions, and effect on the serologic reactions of the blood, intermediat between neoarsphenamine and arsphenamine: an exceptionally low incidence of asymptomatic neurosyphilis as evidenced by spinal fluid examination. In subsequent investigations covering period of eight years, this position has been reasonably well maintained. It would appear that the superior clinical effectiveness of the drug must be measured against an undoubted tendency t dermatitis and hemorrhagic reaction, which is relatively rare with mapharsen for example. Givan and Villa, employing triosdarsen in congenital syphilis, reported it well tolerated by the intravenous and intramuscular routes, and particularly free from paravenous infiltration hen the drug as delivered outside of vein. Gastro-intestinal reactions are more numerous than the verage, but are ttributed by these observers to fright on the part of the children. The drug can be substituted in patient having reactions t neoarsphenamine. It was markedly effective in the treatment of interstitial keratitis, and an unusually high reversal of positive Wassermann reaction (76 per cent) was secured by the use of the drug alone or in combination with other drugs. The tonic effect as notable.

THE PENTAVALENT ARSENICALS

Tryparsamide.—This drug, the sodium salt of N phenyl-glycineamide-p-arsonic acid was synthesized by Jacobs and Heidelberger of the Rockefeller Institute in 1917 It is a white, odorless, crystalline substance readily soluble in water and contains 25 1 to 25.5 per cent of arsenic. Tryparsamide is a relative of atoxyl and derives its therapeutic efficiency and toxic peculiarities, fortunately much reduced, from that fact.

Historical.—For drug in many respects so remarkable, tryparsamide has had slow acceptance in the therapy of syphilis. Thoroughly investigated from the toxicological and pharma

cological standpoint by Brown and Pearce in 1919 It was supplied by the Rockefeller Institute to the Wisconsin group of psychiatrists and pharmacologists, Lorenz and Loevenhart and their coworkers, who in 1923 published the first extended clinical report of its application in its present field, that of neurosyphilis and particularly paresis. Over a period of several years, the Rockefeller Institute maintained control of its distribution and its manufacture was carried out under license by only one concern, Merck & Company The steadily growing clinical experience has now clearly established the fact that the one serious complication (ocular) is controllable, and that prolonged continuous and not casual, intermittent use, is the secret of success with it.

Pharmacology and Toxicology of Tryparsamide.—Brown and Pearce showed the minimum lethal dose for different types of animals to be 0 75 to 2.75 Gm. per kilo a positively unprecedented low level of toxicity for arsenicals with such striking therapeutic efficiency Toxic effects do not begin until relatively close to the minimum lethal dose and recovery from toxic manifestations below the lethal dose is rapid and complete. The drug is remarkably noncumulative in contrast to other arsenicals, and repeated large doses may be given at short intervals without injurious effects. A definite tolerance for it may also be developed All of these findings have been confirmed for man.

The great theoretical interest of tryparsamide for syphilotherapeutics lies in the fact that while it is one of the most powerful trypanocides known, it is only slightly spirillicidal (1–1 or 1–2 as compared with 1–7 or 1–10 for arsphenamine) and will not destroy the *Spirochaeta pallida* to any marked degree in any lesion of the disease. Brown and Pearce in suggesting its use in syphilis, laid emphasis, not on its direct chemotherapeutic effect, but on its tonic action and resistance-building power Subsequent studies by Voegtlin, Smith, Dyer and Thompson employing an ingenious method of testing the penetration of drugs into the cerebrospinal system by studying their action, when intravenously injected, upon trypanosomes introduced into the spinal canal, showed that no small part of the secret of tryparsamide efficiency lies in its extraordinary ability to penetrate the nervous system through the meninges.

Tryparsamide was the most effective of nine arsenicals used, an amount equal to only 4 per cent of the minimum lethal dose being 87 per cent efficient. Mehrtens, Kolos, and Marshall found tryparsamide to be positively chemotropic for nervous tissue as compared with arsphenamine. The spinal fluid of patients who had received previous injections of tryparsamide showed as much as two or three times as great an arsenic concentration as those who had received intravenous arsphenamine injections. The arsenic content of the blood after intravenous injection was studied by Fordyce, Rosen, and Myers, who found that the drug disappeared rapidly from the blood stream, only traces remaining at the end of seventy-two hours, a fact which apparently led them to discount its efficacy

The rate of elimination of tryparsamide is extremely rapid, the relatively enormous dose being excreted, as shown by Young and Muehlberger, to the extent of 68 to 85 per cent within the first twenty-four hours. At least part of it seemed to be excreted unchanged (Young and Hamilton), within twenty-four hours, by the kidney

The distribution of tryparsamide has been shown by Osborne microchemical studies of tissue to be essentially that expected of pentavalent arsenicals, namely high concentration in the nervous system, though the distribution in the rabbit was somewhat uneven and an exemption of the lungs, heart, liver and adrenals was noted. After a lethal dose the drug was demonstrated in sympathetic nerve ganglion and also in the walls of the stomach. Osborne concludes that at the end of an hour following large dose, some arsenic has already penetrated into the nervous system; that the liver is evidently a negligible factor in the metabolism of the drug and that tryparsamide is rapidly excreted through the kidneys and the entire intestinal tract. The increased retention of the drug in the liver late after a lethal dose is interpreted by Osborne as due to primary injury with secondary degenerative effect.

Young and Loevenhart give as the biochemical reason for the production of optic nerve lesions by tryparsamide the general rule, applicable to all arsenicals, that the presence of the amino groups in the para position to the arsenic, regardless of its valence, induces tropism for the optic nerve.

Reactions to Tryparsamide.—Both immediate and delayed reactions to this drug are relatively uncommon as compared with those produced by the trivalent arsenicals. Several reports indicate that there has been a recent tendency for the preparation to induce an increasing number of systemic reactions (Hinrichsen, 1939 Kopp and Solomon, 1940 Beerman and Shaffer 1940 Downs McDermott and Webster 1941) Optic nerve injury continues to be the chief concern of those using this drug. Tryparsamide causes about eight times as many permanent ocular complications in those with damaged eyes before treatment as it does in those with normal eyes before treatment (22.7 per cent and 2.9 per cent respectively Hinrichsen, 1939)

Details of the therapeutic action and side effects including ocular reactions to tryparsamide will be discussed fully in the Chapter on Neurosyphilis.

Acetarsone (Stovarsol, Spirocid)—This is the American official name for pentavalent arsenical with apparently definite spirillicidal activity especially adapted for oral use It is a white crystalline substance, the sodium salt of 3-acetylamino-4-hydroxyphenylarsonic acid. It is dispensed in tablets of 0.25 Gm. each. I spite of the large experimental and clinical literature on acetarsone, summarized in the second edition of this text and in the excellent compilation by Hinrichsen (1942), this drug has not been widely accepted for prophylaxis or treatment of acquired syphilis. Some pediatricians have, however been inclined to consider this drug valuable for congenital syphilis. In the outstanding study by Pillsbury and Perlman (1935, 1939) it was shown that the effect of acetarsone in arresting congenital syphilis is inferior to that of arsphenamine and bismuth preparations the incidence of reactions is high the drug cannot be controlled by experimental studies of spirochetícidal action and toxicity in animals, and it is probably not administered as directed to patients treated at home. For those who wish to use acetarsone it is recommended that the following schemes be employed

For Adults. (*Prophylactic—Non-intensive*) —4–6 Standard tablets daily for three to five days with four to five days of rest between courses. The total dosage is 24–90 tablets (6–22.5 Gm.)

Intensive 4–6 tablets daily for five to seven days with three, later five, days of rest between courses. The total dosage is 100–210 tablets (25–52.5 Gm.)

Therapeutic 4 tablets day seven to five days (total, 49) with four to eleven days of rest (total, 48) Total dosage is 196 tablets (49 Gm.)

For congenital syphilis The system of Bratusch-Marrain was considered by Pillsbury and Perlman as the best available It is low dosage intermittent continuous scheme as follows:

1st week—7 days—0.005 Gm. per kg. daily
2nd week—7 days—0.010 Gm. per kg. daily
3rd week—7 days—0.015 Gm. per kg. daily
For next 6 weeks —0.020 Gm. per kg. daily
Rest for 4–6 weeks.

These courses are to be repeated until the Wassermann reaction, which is taken after each course is negative three times in succession.

Treparsol and Acetylarsan.—These two drugs, the former being the formyl derivative corresponding to stovarsol, which is the acetyl derivative of amino-hydroxyphenylarsonic acid has been employed by Simon, Flandrin, and others with results thus far neither convincing nor satisfactory Gougerot and Lacapere cautiously suggest its use as tapering off treatment. Acetylarsan, the diethyl ammonium salt of stovarsol, may be administered intramuscularly or subcutaneously and was strongly commended by Lacapere and Laurent. These investigators, however rate it as inferior to the arsphenamines and only usable in occasional cases of intolerance of the latter Neither drug has gained any foothold in American practice nor is there any apparent reason at this time for its doing so

Aldarsone.—This pentavalent arsenical synthesized by Raiziss has been studied in the treatment of neurosyphilis by Kamman (1938) and by Spiegel, Leifer and Sarason (1941). It is related chemically to acetarsone and is a condensation product of 3-amino-4-hydroxy-phenylarsonic acid, with sodium formaldehyde sulfoxylate. It is a white crystalline powder containing about 17 per cent arsenic. It is highly soluble in water; the aqueous solution is pink and has a pH of about 7.0. According to the experimental material of Raiziss and his coworkers, aldarsone is more spirochetícidal than tryparsamide. The drug is dissolved in 10 cc. sterile distilled water. The first dose should be 0.5 Gm., subsequently increased to 1 Gm. intravenously at weekly intervals. Only rarely have objective or subjective visual disturbances been observed in patients treated with this preparation, even in those who had previous optic nerve damage (Spiegel *et al.*) or who could not tolerate other pentavalent arsenicals because of visual disturbances. This compound should be given in long courses, similar to those for tryparsamide. Aside from its value as a substitute in cases intolerant of other pentavalent arsenicals, aldarsone is effective in the treatment of neurosyphilis. This therapeutic efficiency has been affirmed by Bennett, Morrison and Modlin (1944) who used aldarsone combined with artificial fever. This combination, however, may produce neuro-ophthalmic complications.

CHAPTER VIII

TECHNICAL METHODS AND CONSIDERATIONS IN DIAGNOSIS AND TREATMENT

General Considerations the Importance of Technic.—The greatest emphasis necessary at the present day in the practice of medicine with respect to the treatment of syphilis is on technic For the physician is constantly bringing modern methods into disrepute through manipulative error and is inflicting injury and failing to cure his patients through his inability to carry out what he attempts The preparation of water the preservation of asepsis, the technic of mixing and the manual and other manipulation of successful administration should be learned for private as for clinic practice. Any physician who administers treatment without personal knowledge and control of these factors may expect trouble. Responsibility can be delegated to properly trained technicians, but even here knowledge necessary to supervise them should be part of the equipment of the physician for the work.

Treatment Room Arrangement and Equipment.—While it is not indispensable to have tiled floors and walls, or the most costly of operating room furniture or even to have a separate room for treatment work, the physician who is called upon to treat much syphilis will find it distinctly advantageous to develop special surroundings for the purpose and the clinic is obligated to do.

The convenience and accustomedness of such working environment adds greatly to technical smoothness and efficiency It assists in maintaining the morale of the patient, and in impressing him in an entirely legitimate y thout frightening him, with the seriousness of his infection and the importance of giving his best cooperation to the effort which is being made t get him well The effect is not unlike that of the well-regulated sanatorium on the tuberculous patient The physical equipment and surroundings of some dispensaries and private offices have as much to do ith the difficulty of holding patients to treatment as do any inherent derelictions of the patients themselves. W have seen enough of the effect of paint clean furniture, organization, and spirit in reviving drooping clinic or building one from small beginnings, to ppreciate that in this aspect of medicine in business, reasonable investment in equipment and personnel brings its return.

The attitude and reactions of the personnel impart as much to the successful operation of a service for syphilis, or an individual practice as does the equipment and the technical skill. Amenities are not mere foibles, but rather the outward evidences of an inward surefootedness, competence and humanity

Cheerfulness, personal friendliness ithout effervescence, the individual rather than the mechanical tone of voice, are technical essentials. The addressing of the patient by name, the recollection of personal details of his case hich shows him that the operator knows who he is and something about his troubles, are invaluable assets in effective treatment work. The patient should never enter the treatment room ithout receiving greeting and smile, if the highest degree of confidence and cooperation is to be obtained

Arrangement.—The light in the treatment room is as important as in the examining room and should conform herever possible t the same criteria. Placement of the table and the position of the patient should be such that no shadow are cast upon the field of work. I intravenous injection it is an advantage t have cross light, hich may bring out the slight elevation produced by an otherwise invisible vein.

A treatment room arrangement which keeps the patient away from sterile tables, solutions and operator and at the same time gives the nurse freedom to control his movement, guide him in and out, reach her sterilizing solutions and bandages and assist the operator without contaminating his field, is a decided advantage

Assistance.—The staff necessary for the operation of a single treatment unit or for private office work need not exceed, in addition to the physician, one unsterile assistant for arsphenamine administration, one or two for all forms of spinal work. It is possible to develop a one-man technic for general or occasionally special practice but it is much more wearing on physician and patient and unsatisfactory if time is important or the niceties of technic are to be observed We do not believe however that spinal puncture should be done on any patient by an unassisted operator even though the patient may be well trained.

Intensive arsenotherapy requires special preparation which will be mentioned later *Military practice can be organized along hospital lines with* individual variations dependent upon circumstances

Asepsis.—The physician will be spared more than one pang of conscience and anxious moment if he can always look backward in his analysis of his own procedure upon the strictest adherence on his part to the principles of asepsis. Clean water long boiling vigorous scrubbing aseptic conscience, are therefore commended as selfish as well as altruistic requirements in syphilological work.

CARE AND HANDLING OF EQUIPMENT

Water for Sterilization.—For the smooth working of syphilological technic it has been our practice to advocate the use of distilled water as the starting

Fig. 102.

THE A-B-C OF WATER FOR ARSPHENAMIN INJECTION

1. Know the source of supply and the chemical treatment of the water you plan to distill.
2. If markedly contaminated, much treated, or subjected to softening or chlorinating processes, use in preference purchased distilled water for chemical work from reliable firm.
3. Test the supply and the end-product from time to time by ( ) boiling it down almost to dryness (b) litmus yellow solution for alkalinity (should not turn red) silver nitrate solution, 1 to 2 drops should leave no cloudiness.
4. Don't rush or bump your stills.
5. Take them down and clean them occasionally depending on the amount of water put through them.
6. Cover rubber with block tinfoil (pure tin).
7. Don't save water by boiling still down. Discard the last third in the still and the first and last fifth of the distillate
8. If still boils dry discard all the product and clean thoroughly all parts
9. Protect scrupulously the mouths of flasks and their contents from dust and exposure to any form of contamination.
10. Make no transfers from flask to flask, after last distillation
11. Use no water over twenty-four hours old.
12. Remember all the time, that the product goes into the blood-stream, and handle it accordingly

point of all sterilization by boiling. Coated and discolored glassware, sticking and uncleanable syringes, ill fitting adapters and needle butts can in this way be avoided and much time and labor saved. There are available types of

syringes and other glassware which successfully stand boiling in distilled water and these types are commended as equipment.

Water for Arsphenamine.—Water for solution of the arsenicals is now obtainable in small amounts in ampule. It is not, therefore, necessary for the practitioner using these drugs to install special equipment for the preparation of his own water. Clinics using large amounts of simple distilled water and desiring to set up their own equipment for it, are referred to the second edition of this text, page 35° for a full description of equipment and methods.

Freshness and Preservation of Distilled Water.—When properly put up in ampule, distilled ater as solvent for the arsphenamines ma be used as marketed without reboiling. This is not true, however of larger quantities of distilled water kept under ordinary conditions in operating room and office. These should always be fresh, made up within twenty-four hours, and must be kept preferably in the ice-box in gauze-corked flasks in which the last distillat is caught. The water should not be transferred about from flask t flask. Before use, freshly prepared distilled water must be sterilized by boiling for ten minutes with the gauze cork removed from the mouth of the flask, and when the boiling is complete sterile beaker may be placed over the mouth and neck of the flask. This is preferable to reinserting stopper.

Glassware.—Glassware used for syphilological work should be heat resistant, preferably Pyrex.

For Neoarsphenamine and Mapharsen Administration Intravenously:

2, 2-ounce heavy-walled medicine glasses.

1 10-cc. or 20-cc. (according to preference) all-glass syringe resistant to boiling in distilled water piston ground t perfect fit.

For Intramuscular Administration of Arsphenamine Derivatives

Only the 2-cc all-glass hypodermic syringe is necessary and the ampule or glass of distilled ater the dissolving being done in the ampule (see Figs. 117 120)

For Tryparsamide Administration.—The same set-up is required as for neoarsphenamine unless the drug is dissolved in the ampule, as with the intramuscularly administered arsphenamines.

Cleansing of Glassware.—Glassware should be washed in green soap and hot water when first purchased, and thoroughly rinsed after each subsequent use. Accessible articles should be swabbed out with a piece of gauze and Florence flasks may be cleaned by agitating in them with a rotary motion mixture of glass beads and scraps of filter-paper in small amount of water. Repeated rinsing in very hot ater followed by distilled water is essential t remove all soap. If pure ethyl alcohol is vailable, this should be used for the last rinsing and the flasks air dried. Denatured alcohol cannot be used.

Autoclaving of Glassware.—Where facilities are vailable glass articles may be wrapped in towels, utoclaved at 20 pounds for half an hour and then baked in the dry oven at 240° C. for one hour. This cannot be done if they have rubber attachments.

Sterilization of Glassware.—All glassware used in intravenous ork should be sterilized by boiling for ten minutes by the clock, after boiling begins, ith water filling and completely surrounding the hollow articles. T immerse flask partly or cover it with wet gauze, in the belief that the steam under the sterilizer lid will sterilize, is mistake. It is economy and safety combined t use distilled water (single distillation) for boiling up glassware, since the deposits of salts and dirt from ordinary water make future cleanliness difficult, if not impossible waste all the value of precaution in water preparation and reck the syringes with grit. All glassware should be wrapped in gauze to prevent bobbing about in the sterilizer with chipping and breakage. Boiling should be slow violent boiling taking toll in breakage.

Syringes.—The syringe is the syphilologist's rifle and selection and care of it should be meticulous and intelligent. Glass syringes should have special care since they are expensive and easily broken. Those which quickly lose the perfection of fit as between piston and barrel do not qualify for satisfactory syphilological work.

Syringes and containers must be carefully cleaned for they accumulat considerable deposits nd surprising residues of the drugs and biological fluids which have passed through them. The

piston and barrel should never be allowed to become separated if several are in use. In boiling the piston is removed and placed side by side with the barrel in gauze wrappings held by properly prepared rubber bands, which prevent both direct contact or bumping. The tip or nozzle of the syringe should be carefully protected in all handling. T "try the suction by putting the finger over the end of the syringe nozzle, while traction is exerted on the piston, costs several syringes mouth when the piston slips from the fingers and flies back. Such maneuver is seldom necessary if proper glass is used and syringe barrels and pistons are not allowed to become mismated. Eccentrically placed nozzles are preferred by some. Glass-metal combinations and elaborate locks are unnecessary though popula both in European and American practice.

Special Precautions.—Schoch's demonstration that enough bismuth arsphenamine sulphonate, for example, is retained in rinsed syringe which has not been thoroughly cleaned, to cause an arsenical dermatitic reaction in patient once sensitized to the drug is in point. The bore of every syringe should therefore be cleansed with cotton wound applicator used as a ramrod and sticky or oily preparations with bismuth residues may well require syringes reserved to their exclusive use. The treatment room chief should inspect the nozzle of the syringe at the point where the needle shoulder comes in contact with the glass, and if any residue can be seen or picked loose with pin, there should be general overhauling of the nursing technic. The junction of the barrel and the end should also be atched. There should be little or no discoloration in properly cleaned glassware. Syringes used for blood dra ing should be immediately rinsed in cold water; if this is mpossible pull the plunger back half-w in the barrel to prevent sticking on coagulation, and clean as soon as possible.

Rubber Including Gloves.—The proper care and preparation of rubber goods before use is essential not only as a matter of economy but because very serious reactions as well as contaminations of solutions and instruments may result from a casual technic. This applies especially to tubing as described below

For the technics here described the rubber articles used consist exclusively of gloves, condenser tubing, corks for condensers, special corks for blood containers in intraspinal work, and the rubber tubing used in connecting needle and container in the gravity administration of the arsphenamines.

All rubber regardless of its use should be as nearly "pure gum as possible, black or transparent yellow (acid-cured) in color and should be prepared, with the exception of gloves, by soaking over night in 5 per cent sodium hydroxide solution in order to prevent "tubing reaction (see p. 296) care being taken to see that the lumen of the tubing is completely filled and washed through with the solution. A crop of tubing reactions appeared on our service even after the published description of the reaction, through the failure of an inexperienced nurse to fill the lumen of the new lot of tubing. After soaking and rinsing, the tubing may be ttached to the containers and sterilized by boiling. Tourniquets and compression bandages require no sterilization unless they are handled by the operator under one-man technic, in which case they should be treated with alkali when new and boiled up with the apparatus.

Sterilization of Rubber Gloves.—The rubber glove is an essential item in the best aseptic technic of syphilological treatment in our estimation, though perhaps this is, with neoarsphenamine or mapharsen for example, an unnecessary refinement

Rubber gloves for asepsis should not be boiled up with the glasses for arsenicals. Dry sterile gloves are decidedly preferable to wet because of the disagreeable and dangerous trick that the wet glove has of leaking contaminated solutions or water over apparatus and int containers and mixing flasks. Gloves should either be boiled for ten minutes, wiped dry powdered with sterile powder and wrapped in sterile wrappers by an attendant under aseptic conditions, or be boiled, dried, powdered, and autoclaved in loose wrappings t 15 pounds pressure for thirty minutes After use, all rubber gloves should be thoroughly cleaned from blood stains, dried and searched for pinholes before being sterilized. T give an examiner or operator pricked glove in syphilological as in surgical work is crime. While these precautions seem part of an elementary technic, it is surprising how much vigilance it takes to carry them through. The physician working alone can scrub up and prepare half dozen pairs of dry gloves at time with less trouble than he goes

through in boiling up and dragging on six pairs of wet ones. In syphilological examinations, f course sterile gloves are rarely necessary

The Gauze and Cotton.—Gauze and cotton must be of the finest type, free from bleaching preparation and sizing of any kind, of long fiber and free from dust or lint.

Cotton Filtration of Solutions.—Loren Shaffer has injected lint-containing solutions into rabbits without apparent ill effects, so that this element in the production of embolism is probably exaggerated, but should, none the less, be carefully w tched in treatment room practice. Solutions which contain obvious shreds of lint should be refiltered through the wet filter W have never seen an embolism from intravenous injection of nonirritating and properly prepared solutions, and believe that this explanation is more often an excuse than a fact.

The Needles.—The needle is a surgical instrument, although its long association with the tailoring trade and the pin cu hion in our minds has perhaps not been the best way to impress us with the fact. Good technical results in syphilotherapy are materially furthered by close attention to minute details in the care and handling of needles, and serious accidents may sometimes be averted by very simple precautions.



Fig. 103.—Testing spinal needle before sterilizing The stylet is removed.

Choice of Needles.—As much care should be given to the choice of needles as t that of surgical instruments, and only the products of the best manufacturers deserve consideration. With the advent of the rustless steels, the softer alloys hich do not take satisfactory points will be less popular nd the precious metals superfluous. The high-grade steel needle requires proper combination of bendabilit and rigidity and should under no circumstances be brittle. Pitting and corrosion of needles under water boiling conditions should disappear with the rustless steel but corrosion by chemical ction must still be closely atched. The eakest spot in the needle is at the junction of the hub and shaft, nd no needle hose length does not allow liberal margin between the point of verage skin penetration and the hub is quit safe, for it is apt to be lost t once on fracture "Preling and the reaming of gritty material from the bore of the needle with stylet, even in amounts only visible ith lens, warn that the needle has become unsafe Internal pitting and corrosion makes the needle dangerous and even the slightest external roughening makes it painful The shaft of needle therefore, should not be placed under the compression of hemostats, the needle being handled instead by the butt, or hub.

The long steel needle must be springy as ell as resistant t fracture and no needle which will not stand bending through an arc of 30 degrees and return practically t normal, is entirely satisfactory The bore must be uniform and the needle must stand the bending strain all the way out t the point (see Fig 103)

Gauge Saf ty Comfort and Speed.—*The gauge of needles must be selected on the basis of* the safety factor; the rat of flow or delivery required the amount of discomfort caused in introduction. The tendency i to forget the first in thinking of the other t factors, especially in spinal puncture needles. An additional factor of technical unfitness arises in the hairline but unbreakable needles hich it sometimes proposed to use bet een the vertebral spines Their

bendability makes them difficult to use. On the other hand, mere thickness does not make needle safe, for the resistance offered by thick needles is greater than that of thin needles. Rigidity or directability is important and here the coarser needle has the advantage over the finer needle. The caliber of the bore not the thickness of the wall, is responsible for the fluid delivery of the needle and should be watched. The wall, not the gross diameter of the needle must be thick enough for safety

Discomfort in the introduction of the needle can be mitigated by the use of local anesthesia with larger needles, but is easily forgotten with those of medium gauge The development of "needle shyness" in patients indicates that this is a distinct factor in their willingness t persist in treatment, and every effort should be made to eliminate these seemingly minor discomforts For this reason, should like to emphasize the utility of the 26-gauge 1-inch hypodermic needle by experienced operators as productive of markedly less discomfort for the patient and as usable in the majority of syringe procedures in intravenous work. A little special aptitude must be developed, but once it is acquired the patient appreciates it.

A small-bore needle such the 26-gauge hypodermic, has importance in forcing the hurried operator to reduce the speed of his i jection. Inasmuch as excessive speed is one of the principal

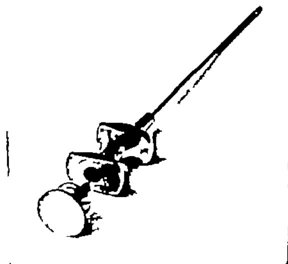


Fig 104 —Detail of the Bier hub. When the stylet is properly seated in the needle the notch in the shoulder engages the pin in the end of the hub

factors in reaction with neoarsphenamine, the small needle tends to prevent trouble on this important score.

Importance of the Stylet.—Stylets should be furnished with all hollow needles and used not discarded.

The occluding or obturator stylet such as is used in spinal needles should be of the same material as the needle, perfect fit, and polished so as not t score the bore. The cleansing stylet need not fit so closely and is usually softer ure of noncorroding alloy It must be long enough to extend beyond both point and hub for effective handling, and rigid enough to stand repeated forcing through the needle ithout buckling or kinking

The occluding stylet of the spinal needle being fitted to the needle and ground ith it should never be separated from it and may be numbered t match it The t should lie side by side, be picked up and laid dow together and fastened or wrapped together with gauze in sterilization Good result cannot be expected where these precaution are neglected.

The Needle Hub.—The hub is the handle of the needle and deserves more than merely passing consideration. If the needle itself is to be handled in the manipulation, the hub should be large enough and heavy enough not to be constant source of irritation. The Luer hub and the majority of cylindric hubs are technically suited only to use ith lever such as that afforded by the syringe to which they are fitted T use Luer needle by direct manipulation seems need

lessly difficult. If the needle is t be handled direct, as in spinal puncture, it deserves suitable h b. T handle any needle by the shaft because the hub is unsatisfactory sacrifices fundamental principle of needle asepsis—never to touch the shaft, even with sterile gloves. For these reasons, all the needles on our service that are handled direct and not through the intermediation of syringe or tube have Bier hubs (Fig. 104) or should be fitted with guard as in the Fordyce or the Schreiber needle. A rubber tube may be attached to needle hub for routine blood-drawing work.

While hubs are now practically universally adapted to syringes, it is best to use syringes and needles by the same manufacturer if possible. If they do not fit perfectly and invariably without wabbling or aspiration of air or leakage of fluid, the product should be discarded and complaint made Endless vexation will otherwise result. It should not be necessary to use adapters for other than tubing connections. In the purchase of needle it is well t have a syringe or adapter t hand to insure fit, and not to trust t impressions or recollection.

In the spinal needle it is particularly important for the types of point here described, that the obturator stylet be a perfect fit and be held rigid in the barrel. Obturator hubs, carrying pins which fit into holes in the Bier hub, are ultimat ly unsatisfactory because they clog, cannot be kept clean, and ultimately no longer satisfactorily receive the pin which holds the obturator stylet in place. In order to overcome this difficulty longer pin fitting into an open slot in the Bier hub has been developed by one manufacturer and apparently gives more rigid fixation of the stylet while permitting the proper cleaning of the needle.

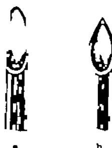


Fig. 105 —a, Rounded needle tip, with cutting edge, which makes an incision in the vein instead of puncture. Less desirable than b, the pointed needle, which inflicts less trauma and diminishes the possibility of leakage

The Needle Point.—The point is to the needle what the edge is to the scalpel and it deserves the same deference and consideration. A five-diameter lens and a good light are indispensable to the proper examination and care of a needle point. In all cleaning and manipulation of needles the point should be protected. The slightest contact of a point with a hard substance unaware may change the next use of that needle from sleight-of-hand to bungling Needles have both point and cutting edge, and the proportion which one bears to the other makes a decided difference for the entered tissue In a technical publication (1017) on intravenous injection, Stokes called attention to the effect of the cutting edge of a needle in producing a leaking venipuncture (Fig 105) Greene, whose spinal needle point is illustrated in Fig 100 has since shown the same thing to be true of dural punctures in spinal work, and his findings were confirmed by Loren Shaffer Bloody arms after vein puncture may therefore be regarded as technical errors and traced to the operator who should be responsible for his needles.

Some common defects in needle points are shown in Figs. 107 108. They are often only detectable by feel or with a hand lens, but they make a decided difference with the patient. It should be recalled that the fitted stylet forms part of the needle point and must be exactly mated to form it, as in the spinal

needle. Such a needle as A in Fig 107 or E in Fig 106 will tear or punch out tissue with pain and leakage as consequences

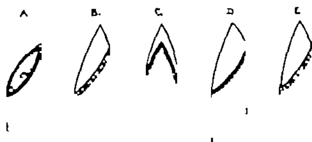


Fig. 106.—(A) The short bevel spinal or cistern puncture needle (B) the Greene or conical point (eccentric) in profile (C) posteriorly (E) shows worn or misfitted stylet which exposes the cutting edge of the needle, cutting or tearing the dura, though a properly made point makes only puncture, with little leakage.

The Greene point for spinal needles (Fig. 100) can be ground from the ordinary flat-bevelled needle by hand on a wheel or stone, or can be specified



Fig. 107.—A, The point of spinal needle with an improperly fitted stylet, such needle tears the dura. B, The proper bevel for spinal needle point. C, The proper bevel for cistern puncture needle.

for the type of needle having the hub shown in Fig 104 Corrosion, which formerly made these very shortlived, can now be avoided by the rustless steel.

The Needle Bevel.—The bevel of a needle point varies with its use Where mere easy penetration of tissue with little discomfort is desired, as in intra

muscular injection, the longer and more lancelike the bevels short of the risk of fracturing or turning the point, the better On the other hand, if restricted space in a tube about the needle point, as within the lumen of a vein or in various parts of the spinal canal forms part of the working condition the bevel must be shortened. In Fig 109 three types of bevel often found on intravenous needles in actual use are shown The first is too blunt for easy entry the second so long it catches in the far side of the vein the third is correct. The longer bevel of the lumbar as distinguished from the shorter bevel of the cistern puncture needle is shown in Fig 107

Needle Sharpening.—Needles do not retain point or edge indefinitely though the fact is easily forgotten. I fact, it is ell to retouch needle to the proper edge and point ith each five to ten punctures. Spinal needles are most satisfactory if touched up before each puncture Retouching ma be needed on an improperly bevelled new needle. In the office, retouching and



Fig 108.—Feathered and "fish-hooked" needle points. The turning of the point may be so slight as only t be detected with lens

sharpening should be done on hard Arkansas oilstone and care must be taken to void feathering or frazzling of the inner edge nd the production of flat bevel The motion necessary t point hollow needle ith suggestion of concavity which should always be present on ne needle, is produced by pressure being brought to bear on first one side of the point and then the other I clinic practice, Colonel Harrison recommends ½-inch finest carborundum wheel with similar-sized lead heel as finisher both being operated by water motor, not by electricity Feathering of the point in sharpening and "fish-hooking" from turning of the point must also be watched The needle should be tested for its "bit" when laid flat on the skin of the hypothenar eminence of the palm. If it takes hold ll there, it will penetrat vein ithout cutting or stripping I sharpening spinal needles, the stylet must be kept forced in, so that the operation requires one hand at the point, the other t the hub.

"Fish-hook" turning of the needle point in contact with hard objects and too much pressure in sharpening ("feather") even when too slight to be seen can be detected by drawing the needle in its long axis on the flat across a piece of gauze. This should be done for all intravenous and intramuscular needles before sterilization and sometimes after if there is any doubt. The resistance and jerky pulling can be easily detected. If in doubt, examine with a lens. Such needles stick, tear and are very painful and may break under "jabbing" and forced manipulation

Care and Cleaning of Needles.—Needles should never be bunched and thrown into solutions but handled individually. After use the needle should be rinsed immediately with some non-coagulable solution, for every time blood is allowed to clot in a needle a certain amount of solid residue is left to plug and favor the retention of moisture and infectious material. In time this material cannot be removed with a stylet. Every needle should be as carefully reamed out with its stylet as if it were a gun barrel. If an aspirator or filter pump is at hand, clean water followed by alcohol and ether should be drawn through the needle to dry it completely. If this cannot be done, alcohol and ether can, with a little care, be poured or tapped through the larger needles by tapping with the finger over the opening in the hub when it is filled with alcohol or ether. The points of needles should in general be sharpened before cleaning, not after (to remove any accumulation from the bore. The external surface of needles should be kept polished with a non-scratching powder, and special attention should be given to the cleaning of the hub with a blunt applicator and gauze. Oil is no longer necessary on rustless steel, but if it is used it should always be removed with alcohol or ether before sterilizing the needle. The unsatisfactory fit of a needle after use may be due, not to warping or manufacturing defects, but to coagulum that has not been properly removed from the hub. The stylet of a spinal needle should be handled in the same way as the needle itself and especially protected from kinking or bending, which then and there ruins the fit at the point.

Sterilization of Needles.—Merely dropping a needle into a disinfectant solution or even boiling it a few moments does not sterilize, as we have been able to satisfy ourselves bacteriologically. The bore of the needle, especially if small, may moreover be unaffected even in boiling because of the contained air bubble. This is especially true if oil be used in cleaning. Alcohol or

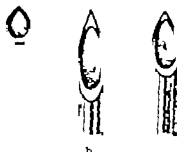


Fig. 100.—Three types of needle point. *a*, Too short; *b*, too long; *c*, correct.

ether should be drawn through just before boiling and should not contain any corrosive or oily denaturing agent. When the needle is boiled, water can thus gain access to all parts of the bore. Such needles should be boiled without the stylets. Sterilization by boiling requires ten minutes and distilled water should be used by preference. Sterilization by baking at 210 C. for forty-five minutes should be used for intraspinal treatment needles, which are wrapped in gauze and sterilized in plugged test tubes. Spinal puncture needles are sterilized by boiling.

Types of Needles.—The improvement in the characteristics of steel is making possible an eminently justifiable trend toward small needles in every form of manipulation. Thus the gauges may be revised downward, the ordinary spinal needle being now 20 gauge, which is, however little flexible for the inexperienced, and the 16-gauge blood-drawing needle being used only occasionally. The 26-gauge hypodermic needle is now preferred in my practice to the 20-gauge intravenous needle and the 22-gauge needle is quite satisfactory.

For intramuscular work, using the aspiration test 20- to 22-gauge needles, 1½, 2, and 2½ inches from the tip of the hub to the point are recommended according to the thickness of the buttock. In the huge buttocks of obese women, a 20-gauge spinal needle is sometimes invaluable.

Special Considerations Regarding the Spinal Needle.—The reduction of seepage from the meningeal puncture wound, has brought forth a number of modifications. The Hoyt needle encloses the inner shaft in an outer sleeve, the stylet fitting the inner shaft. The inner shaft is longer than the outer and when the outer or penetrating needle reaches the dura, the inner needle is advanced to puncture it. This device has been favorably reported as reducing the incidence of headache, but causes delay and tactile uncertainty in the inexperienced and on routine work. Tapering the point, as in some French types of needles, always involves the risk of fracture. The Pitkin point, a very flat bevel, is intended to leave a small "lid" of dura adherent to one marg

of the puncture hich acts as flap closure W prefer the Greene type of point which leaves a structurally simple and sound needle whose antileak qualities have been experimentally demonstrated.

Testing of Needles to Prevent Breaking in Use.—Figure 103 illustrates the method of testing the spinal needle with stylet removed

The hub is held firmly in the right hand and the shaft laid on the ball of the thumb, at the junction of shaft and hub. The index finger is then pressed down on the needle and bending stress sufficient to carry the shaft through an angle of 45 degrees is applied as the fingers are drawn from the hub to the point of the needle. W have never known needle which would stand this test to break in use, and it should be routinely applied once week during cleaning to all needles which are subject to heavy usage. The same test may be pplied t intramuscular needles The weak point of shorter needles is at the hub, and in the case of the Schreiber just pointward of the guard, so that the Schreiber should not be ground down too short to allow good safety margin outside the vein.

The lif of needle cannot well be measured in time, and depends much on the care which it receives. It is better t discard a spinal needle after fifty punctures than to wait until it breaks, either in testing or on the patient. N spinal needle which has been sharpened down so far that it does not leave 1-inch margin outside the skin when the dura is entered, can be regarded as entirely safe.

THE PREPARATION OF THE ARSENICALS

Remarks on Technical Systems.—The ensuing sections of this chapter outline essentially systems which have been found to work successfully in large numbers of cases and which are the products not only of thought applied to our individual methods but in comparison with the methods of others. On the other hand it is well realized that personal modifications very properly develop to fit special aptitudes and situations and that to talk of standardization to those who are already experts, is, of course, a work of supererogation

But system on service of any considerable size makes it possible to trace mistakes. If it is founded on sound principles, it fits the large majority of those who are called upon to use it If speed and technical accuracy are essential, it meets the need and spares the patient. It furnishes definite scheme of teaching and basis on which the beginner can align his own work I the instruction of medical students it is very helpful. N one should be asked t discard method which gives him completely satisfactory results, but the inexperienced can at least gain something by consideration of principles and fit their practice to them or the reverse, as best they can. Our system and equipment are offered only as one of many nd for what they are worth.

Preparation of the Arsenicals—Know the Ampules on Sight.—Every user of the arsenicals should familiarize himself with the color odor consistency and solubility of the preparations he expects to use. He should see the ampules in their original wrappings and should read every word of the labels. While he is familiarizing himself with the work, he should under no circumstances allow a nurse or assistant to open or prepare his ampules. To delegate any of these responsibilities to others, before he himself becomes so expert that he can recognize the drug and solution he is working with by instinct and on sight, is to take an unjustifiable risk for his patient.

Sterilization and Detection of Flaws in Ampules.—The ampule containing the drug should be immersed completely in 95 per cent alcohol (a denatured alcohol containing no metallic or methyl alcohol denaturing agents is allowable) It should be allowed to soak in alcohol for thirty minutes before use This will sterilize the surface will slightly moisten the contents, if there is a crack or perforation, and will reveal a very fine crack if the powder be shaken

around in the ampule before opening If there are any imperfections, the ampule should be discarded or returned to the manufacturer

The Ampule Label.—Removal of the pasted label on the ampule depends on the circumstances under which the drug is used. In large services manned by experienced operators who are perfectly familiar with the drugs, and in which fixed dosages are regularly employed, the labels should be removed by soaking in water or scraping before disinfection in alcohol, because of the slight possibility of glass defect beneath the label. The individual user less familiar with the drug, is wiser to keep the label intact and sterilize it with the ampule, far as possible, so that he may know at any and all times what he is dealing with by simply glancing at the label. Under such circumstances, he should handle the ampule with sterile forceps and piece of sterile gauze, after he is scrubbed up.

The ampule label carries the manufacturer control number of the drug and should be preserved either as matter of record or to trace complications and difficulties. It is rarely needed, but when actually needed is usually missing. It is our custom to record in a treatment book the lot number of each preparation used and t whom it as administered.

Preparation of Arsphenamine (606) for Administration.—Arsphenamine (606) requires neutralization before administration. An effort is being made to facilitate this by dispensing with the drug a ceresin or paraffin-coated vial containing the precise amount of sodium hydroxide of standard strength necessary to neutralize the dose of "606" which it accompanies. This device originated by Raiziss and employed by Cannon (1939) in his simplified technic for administering old arsphenamine, is a great saving and convenience and materially simplifies the most vexatious feature of the technic. Where this is not used, the following specifications for the sodium hydroxide solution must be heeded

Normal sodium hydroxide solution is employed in the neutralization of arsphenamine solutions in accordance with the standards of the United States Public Health Service, the concentration being determined by titration against normal hydrochloric acid solution. A normal NaOH solution is approximately 4 per cent, but if made up by weight, the absorption of water by the salt makes the molecular concentration very uncertain and exact quantitative neutralization is impossible. If it is impossible to secure titrated solution, 4 per cent solution may be used The NaOH must be chemically pure and the water used in making up the solution should be the same as that employed for arsphenamine administration. The older drop neutralization technics specify freshly prepared solution and 15 per cent concentration. In order to keep sodium hydroxide solution it is necessary to use glass-stoppered bottle coated with paraffin or ceresin as above described. In any case, it is not advisable to make up more than week supply of the solution at time, unless it can be kept in closed buret system. This protects it from absorption of moisture and carbon dioxide as well as from the glass. The solution is self-sterilizing. In the office, where only occasional injections are given, 4 per cent sodium hydroxide solution may be freshly prepared, boiled in large resistance glass test tube and used t once (drop method)

The Intravenous Administration of Arsphenamine (606)—Inasmuch as good deal of manipulation is involved, it is advisable for the operator to scrub up as for surgical procedures putting on sterile gown and dry sterile gloves. The mixing flasks are then rinsed with the specially prepared water at the temperature recommended by the manufacturer in the direction, accompanying the ampule. In present practice, water at room temperature is preferred to hot ater If the flasks are capped so that their edges are sterile which is the preferable method, direct pouring from vessel to vessel is possible The filter cotton is placed in the funnel and rinsed with sudden douche of specially prepared water and the cylindrical container (Fig 110) or buret is rinsed, filled with sufficient ater t wash out the rubber tubing thoroughly and assure its being filled ith ater (raise and lower repeatedly nd squeeze to be sure all air bubbles are dislodged). The ampule is then removed from the alcohol, thoroughly dried th sterile gauze, special attention being given to the neck, filed and the tip struck off It is not desirable to have too large an opening, hich will dump the drug on to the bottom of the flask to form difficultly soluble bolus. Instead, the drug should be sprinkled around the sides and bottom of the wet flask. Ten cc. of specially prepared water per decigram is then poured into the flask and by rotary swinging motion, the arsphenamine rapidly passes int solution ithout shaking or aeration.

As soon as the arsphenamine is completely dissolved (and there should be no residue), if the solution is perfectly clear and of normal odor (to be learned only by experience), neutralization may be begun. Solutions which have a very pungent and penetrating smell or which are even slightly cloudy or opalescent are unsaf and should not be tinkered with but discarded.

Neutralization Technic.—The neutralization of the arsphenamine solution may be accomplished by three accepted technics which are roughly or exactly quantitative, as distinguished from the older qualitative technics. Neutralization to form the disodium salt with an untitrated sodium hydroxide solution may be performed by counting the number of drops or droppers full of the solution required completely to precipitate, and completely to redissolve the yellowish-white arsphenamine base. One fifth t one fourth more is then added and we have even used little as one sixth, with satisfaction. While this procedure does not give even an approximation to quantitative production of the disodium salt, it gives very satisfactory mixture of the mono- and disodium salts for ordinary use. The method, however is difficult and unsafe for the inexperienced and properly displaced by exact quantitative neutralization with titrated solutions

Quantitative neutralization by the buret method may be used with either a titrated normal or an untitrated (4 per cent by weight) solution of sodium hydroxide. T produce the disodium salt with titrated solution of NaOH, add an amount representing 0.85 cc. for each decigram of the arsphenamine used, regardless of the amount of water in which the arsphenamine is dissolved. Thus, for 0.3 Gm. arsphenamine, 2.55 cc. of NaOH solution is added for 0.4 Gm., 3.4 cc.; for 1 Gm 8.5 cc. and so forth. If slightly less alkaline mixture of mono- and disodium salts is desired, 0.75 t 0.8 cc. normal NaOH solution per decigram is added. The calculated amount of the NaOH solution should be added all t once. To produce the disodium salt with roughly prepared 4 per cent solution but one in reality of uncertain strength, add small amounts from the buret until the visual end-point is reached, using essentially the same procedure as with the dropper technic.

The pH of the properly prepared arsphenamine solution varies from 9 to 10. The solution should be perfectly clear without trace of precipitate or cloudiness. On allowing solutions to stand, after the older methods of neutralization, they would occasionally "fix back" to slight opalescence, indicating the presence of the base, which could be cleared up by adding drop or two of the alkali, but with quantitative neutralization, no such phenomenon should occur If it does, it indicates something seriously wrong with the drug or technic, and the whole situation should be gone over and the solution discarded. Look especially to the strength and purity of the NaOH.

Inexperienced operators should test their solutions with litmus, transferring drop on sterile glass rod to piece of litmus paper (do not touch rod to paper) in order to obtain visual evidence of the series of reactions through which the preparation passes. On the other hand, it cannot be too strongly stated that only the dangerously ignorant or foolhardy will attempt to "tinker with an incorrect arsphenamine solution or to administer solution which has not behaved normally The addition of hydrochloric cid to solution which is supposedly overalkalinized cannot be too vigorously condemned. Only solution hich the operator believes to be prepared *secundum artem* up t the moment of injection, should go into patient vein.

Reduction of Toxicity by Standing.—When the solution of arsphenamine has been completely alkalinized, it should be set aside from thirty minutes to an hour the top of the mixing flask or the container being covered with sterile beaker or watch glass.

The Container.—The finished arsphenamine solution may be poured at once into the container or allowed to stand before pouring The cotton-containing funnel is used for filtration. After the solution is poured in, specially prepared water is poured through the cotton to wash the filter and to make the solution up t the proper concentration of 20 t 25 cc. per decigram of the drug In clinic practice, volumes of solution as high as 5 to 10 Gm. of the drug may be made up at time (5 Gm. t the liter) and poured through the filter as needed. The tip of the rubber tube, with its adapter should be kept sterile.

Wastage occurs in all manipulations except neutralization and in practice is provided for by allowing an excess of one tenth in mixing over calculated needs. It is better to have little left over than to skimp the doses.

Preparation of Neoarsphenamine for Intravenous Injection.—Neoarsphenamine should be kept in a cool, dark place, preferably a refrigerator Only one dose should according to standard instructions, be prepared at a time. Only the preparation for the syringe technic is described. The equipment consists of a supply of the freshly prepared water in flask or ampule two

medicine glasses (Fig 113) and the syringe shown in Fig 112. Neoarsphenamine ampules are rarely large enough to mix the drug in ampule and in safe

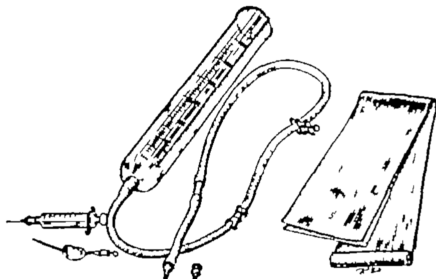


Fig. 110.—Single buret (300 cc.) for gravity administration of arsphenamine, fitted with tubing, pinch-cock, screw clamp, glass tell-tale, and adapter Syringe for local anesthetic, Schreiber needle, and band tourniquet.

concentration In all handling of syringes and glass, whether with or without sterile gloves, the operator should not touch the inside of the glasses or that





Fig. 111 —Convenient form of spring clamp, made of nickel-plated brass which can be sterilized by boiling.

part of the piston of the syringe which enters the barrel. Precautions with reference to the ampule and inspection of the drug should be strictly observed

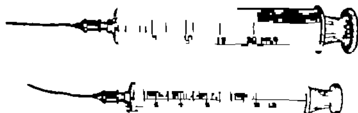


Fig. 112.—Types of syringe used in intravenous neoarsphenamine and intravenous mapharsen administration. Note that in attaching the needle the bevel should be toward the graduations and the needle introduced bevel up. The curved needle can be bent t adapt it to angular surfaces as about the jugular and cephalic veins. The guard is omitted in our recent work, the syringe barrel being controlled by the right hand and the piston by two fingers of the left.

After flushing the lip of the flask, specially prepared water at room tempera ture is poured into one of the glasses or the water from an ampule poured into

it. The ampule of the drug is opened after careful wiping of the neck, and the dry powder poured into the other glass. If preferred the requisite amount of

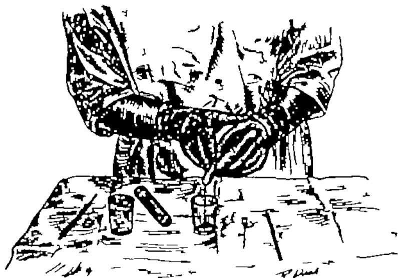


Fig 113.—Equipment required for the administration of neoarsphenamine. The specially prepared distilled water is in the medicine glass to the left, and the drug is prepared one dose at a time

water (10 cc.) may be aspirated by the syringe after rinsing, and discharged into the second glass, the neoarsphenamine powder being poured upon the surface of the water But the pouring of the water on the drug is preferred for

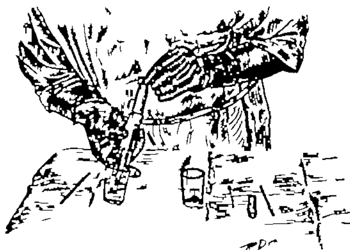


Fig 114.—Preparation of neoarsphenamine for intravenous use. The powder is in the right-hand medicine glass, and the required amount of water is poured upon it from the syringe

the powder then remains in the bottom of the glass instead of floating about the syringe By slow and careful aspiration and ejection of the water without spurting or bubbling the neoarsphenamine is completely dissolved (Fig 115)

The *incorrect* method of dissolving neoarsphenamine by holding the syringe with water at a distance and squirting it to produce a froth, thoroughly aerates

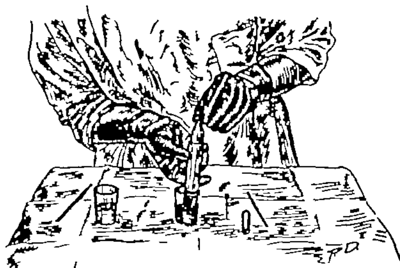


Fig 115.—Proper method of hastening the solution of the neoarsphenamine, by gently aspirating and expelling water with the nozzle of the syringe always below the surface to avoid bubbling.

and toxifies the drug, as shown in Fig 116 It is always the mark of a greenhorn to squirt neo solution or solvent. When the drug is completely dissolved the

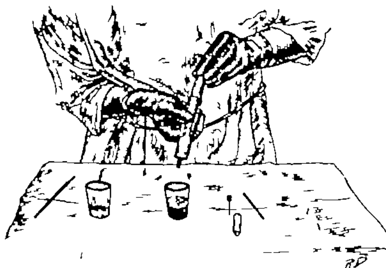


Fig 116.—Neoarsphenamine should not be squirted since aeration increases toxicity Mapharsen should be squirted since aeration decreases its toxicity

solution is inspected to be sure that there is no residue. Rapidity of solution and absence of residue are the most important protections against the mistake of injecting arsphenamine instead of neoarsphenamine a blunder unfortu

nately made in the best clinics, occasionally The glass should be held to the light for certainty in this matter A properly made neoarsphenamine should go into solution within two minutes, although the U.S.P.H.S. standards allow as much as twenty minutes. If solution is incomplete the drug should be discarded. Not more than twenty minutes should ever elapse between solution and administration, and it is preferable to give the injection at once. The medicine glass should be thoroughly rinsed after the mixing is completed and none of the drug held over for more than ten minutes to the next mixing If a second ampule must be mixed to complete the dose from the remnant of the first, a third medicine glass should be used and the second solution judged on its own merits.

Filtration of neoarsphenamine solution is usually unnecessary If desired, aspiration may be made through a small needle to exclude gross particles.

After the solution has been drawn into the syringe through the needle, all the air is expelled as the syringe is held vertical. Intravenous injection is then carried out in accordance with the technic described on page 309

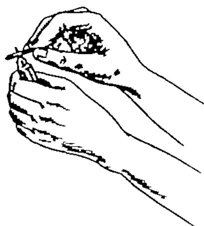


Fig. 117 —Ampule technic for certain arsphenamines. Opening the ampule (After Cazelman)

Preparation of Mapharsen Solution for Intravenous Injection.—*Single Dose Ampules* (A) Mapharsen solution may be prepared directly in the syringe if desired. Draw ten cc sterile distilled water into a syringe to which an intravenous needle (preferably 21 gauge) is attached. Expel approximately 1½ cc. of this water into the single dose mapharsen ampule, then draw the solution back into the syringe. Repeat this several times or until the mapharsen is completely dissolved Finally to complete mixing and to remove free carbon dioxide draw air through the solution in the syringe several times. The solution is then ready for injection

(B) Mapharsen solution may be prepared by adding the contents of a single dose ampule to 10 cc. of sterile distilled water in a sterile glass container stirring vigorously until completely dissolved The solution may be freely aerated by drawing into and expelling from a syringe several times.

Hospital Size (10-dose) Ampules Dissolve the contents of a 10-dose ampule (0 4 gm. or 0 6 gm) of mapharsen in 100 cc. of sterile water Stir vigorously and fill syringe with amount of solution necessary to contain the required individual dosage Ten cc. will contain a full dose, five cc. a half dose etc.

Mapharsen or dichlorophenarsine hydrochloride solutions may be allowed

to stand for several hours exposed to air with no increase in toxicity or loss in efficacy

Silver Derivatives for Intravenous Injection.—Since there is decided difference between the composition of silver arsphenamine, sodium silver arsphenamine and neosilver arsphenamine



Fig. 118.—Injecting the solvent, thus dissolving the drug.

the instructions of the manufacturer should be followed. Salt solution, 0.4 to 0.8 per cent, must be added in various technics after dissolving the drug in cool water The solution should be of bright and sparkling brown color not turbid or muddy which indicates an oxidized drug.

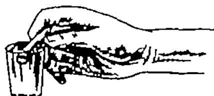


Fig. 119.—Allowing ampule to stand, with shaking (*not with neoarsphenamine*) to insure solution. Inspect for undissolved particles.

Ampule Technic for Intramuscular Administration of Sulpharsphenamine and Bismuth Arsphenamine Sulphonate.—The ampule of the drug is inspected and prepared as in the case of other arsphenamines. The only equipment

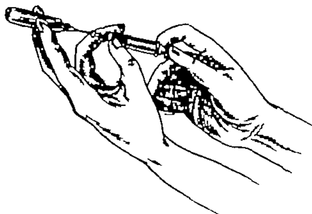


Fig. 120.—Refilling the syringe for injection after solution. Change needle before injecting

required is a 2 cc. all-glass Luer hypodermic syringe graduated in cubic centimeters, needles for intramuscular use, and a sterile medicine glass containing the specially prepared distilled water One and one half to 2 cc of the water in accordance with the manufacturer's directions, is aspirated through the

needle into the syringe and then injected into the ampule containing the drug The technic of handling ampule and syringe is shown in Figs. 117–120 The drug can be aspirated back and forth a few times and agitated without fear of aeration and when completely dissolved is drawn up into the syringe *There must be no undissolved particles, and a fresh, dry needle should be* used in injecting the drug—not the needle used in preparing the solution. None of the unused solution can be held over for a subsequent injection Maximum doses are often wisely divided between the two buttocks.

If a local anesthetic, such as butyn, has not been added to the ampuled water employed in preparing the drug for injection two to four drops of a 4 per cent butyn solution may be added after the drug has been dissolved in the ampule

THE TECHNIC OF INTRAMUSCULAR INJECTION

Importance.—The importance of an exact technic in intramuscular injection soon becomes evident on questioning patients who have given up treatment prematurely An unsatisfactory technic of intramuscular injection is quite largely responsible for the practitioner's difficulties in carrying through a modern treatment regimen, and with other causes, ranks, according to the observations of Pugh *et al* as one of the weak points of modern clinic methods. The older suggestions as to rational procedure were largely empirical and only recently in this country by Zwick and Batson and by Shaffer has a genuine effort been made to determine the rationale for the procedure. The technic here offered was originally designated as epifascial in accordance with the terminology of Wechselmann but it has since been shown *by Shaffer that it is in* reality intramuscular and that the term epifascial should be discarded

Intramuscular injection is, in our experience best performed by women technicians and nurses who are lighter of hand and more dexterous than men. Large men are particularly apt to be heavy-handed and ungentle and patients frequently protest their ministrations in intramuscular injections Deftness of touch and speed of action are both essential.

Site of Injection.—Shaffer in particular showed that the site of injection should bear intelligent relation to the anatomy of the underlying parts that only in one region of the buttock, for example was a minimal reaction to be expected—namely the upper outer quadrant. He showed that the drug suspension should be delivered deep into the body of the muscle that it spreads itself longitudinally along the fascial bundles (in the case of the gluteus maximus diagonally across the buttock from within outward and downward) and that the leaking-back of the emulsion along the needle track could be reduced by keeping the needle in place for at least a minute following the injection. The rate of distribution depends somewhat upon the medium, oily suspension being slower than aqueous. Pain down the leg following injection in the buttock, is, in Shaffer's opinion, due to irritation and injury of the lesser rather than the greater sciatic, as has previously been supposed

The buttock should always be palpated for old infiltrations and tender spots before an intramuscular injection is given and it is well to ask the patient if he has ever had sciatica or pain down the leg before giving the first injection. The first 3 or 4 injections of any intramuscular preparation are almost invariably painful and several small doses are sometimes recommended at one-day intervals before a regular course of intramuscular injections is put

under way in order to "harden or toughen the buttock. The initial discomfort soon disappears

The site of injection in intramuscular work should be sterilized either with iodine, which, however may set up irritation and which corrodes and pits needles or preferably by vigorous scrubbing with alcohol until the skin is red.

Two additional points have had strong emphasis from recent investigations an active muscle is a much better site for intramuscular injection from the standpoint of absorption and general quick recovery than an inactive muscle, and massage following injection is one of the most important preventives of local reaction and accelerators of absorption available

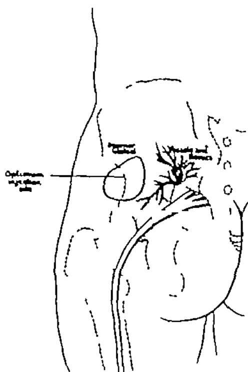


Fig. 121 —(After Shaffer.)

Other sites than the gluteus maximus may be employed for intramuscular injection, including the infraspinatus muscle and the deltoid, but these are relatively unsatisfactory both on the score of slow absorption and materially increased pain from the majority of modern antisyphilitic medicaments. Deep subcutaneous injection has been advocated for sulpharsphenamine (subscapular by Casselman, deep subcutaneous by Arwyl-Davies)

Procedure —The technic here described applies particularly to the use of the buttocks In Fig 121 are shown the anatomical structures involved in their relation to the surface outline, and from this it becomes apparent that injections delivered near but not at the inner angle of the upper outer quadrant, the needle being introduced vertically have the best outlook for uneventful absorption If delivered too far toward the crest of the ilium, the needle may strike bone or obstinate pain may result, and if too close to the central point of the quadrant, one or both sciatic nerves may be involved. The upper inner

quadrant is open to the same objection and the patient sits on both lower quadrants, thus materially increasing his annoyance and discomfort.

Instruments.—These have been described on page 297 (Figs. 112, 122) The caliber of needle will depend somewhat on the thickness of the suspension, 22-gauge needles being used for aqueous solutions, 21-gauge for oil suspensions.

Sterilization.—Needles and syringes are preferably sterilized by boiling for ten minutes, though pure alcohol may be used, if necessary

Preparation of Emulsions.—Suspensions of insoluble drugs require most thorough and systematic shaking whether in ampule or in bottles. Preliminary warming is useful in most preparations and actual heating necessary in some the manufacturer s directions to be followed in this matter Cole, and his co-workers have shown that under routine clinical conditions the amount of drug in the suspension may vary greatly between the top and bottom of a bottle, even after supposedly proper shaking A useful clinical test is to turn the container upside down to see if any adheres to the bottom If it does shaking has been insufficient.

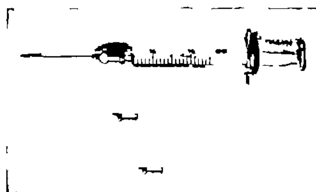


Fig. 122.—All-glass Luer syringe, with the various sizes of needles used for intramuscular injection.

Beerman adapted the Kahn shaker in common use for the laboratory test to the shaking of bottles of heavy suspension. The container should be repeatedly shaken at intervals for periods of two or three minutes throughout forenoon work and suspensions should not be allowed to remain in the syringes long before they are injected.

The Needle.—In general it is desirable to employ a clean dry needle for the introduction of a suspension and the question as to whether or not the needle should contain the emulsion becomes academic when the aspiration test presently described is used. The external surface of the needle, however should not contain the slightest traces of the drug to be injected, for this is a frequent source of skin infiltration and discomfort. It is desirable also to empty the needle into the tissue before withdrawal by carrying an air bubble between suspension and piston which can be injected through the needle into the muscle, thus clearing it completely without the slightest ill effect.

Posture of Patient.—Intramuscular injections may be given with the patient standing or lying face down, preferably the latter A sitting posture is described by Cornbleet (1939) self-administration by Waugh and Heering Women should remove their corsets, for the snap of a pulled-back girdle, striking the hand, has, in our experience broken a needle. The patient should relax by turning the head away from the operator and the posture of "toeing-in to

relax the gluteus maximus is shown by contrast with the effect of "toeing-out in Fig 123 It is advisable always to warn the patient, for a sudden jerk or twitch may break a needle. When warned he may be instructed to draw a deep breath. Allowing the arms to hang over the sides of the table further induces relaxation and prevents stiffening of the buttocks

Needle Entry—The position of syringe and needle as held by the right hand is shown in Fig. 125 The left hand is placed flat on the buttock as shown in Fig 124 and the skin and superficial tissues then drawn downward by traction. On release these tissues provide the valve that prevents leakage along the needle track Two motions are possible for the introduction of the needle (Fig 125) one a dagger-like stab whose quickness makes it relatively painless but which has the disadvantage of lack of control and increased danger of

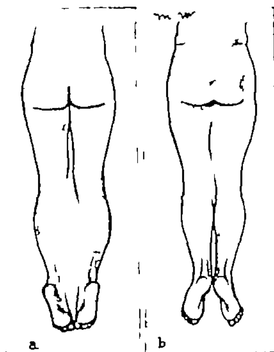


Fig. 123—a, "Toed-in to show the relaxation of the buttock, b, "Toed-out with the dimpling of the buttock indicative of a tense musculature

breakage the other a resting of the side of the hand upon the skin to steady it, a placing of the needle point almost in contact with the surface, and then, by a quick twist of the wrist, a passing of the needle through the skin. This with a little practice can be done very rapidly and the remainder of the entry is painless and can be made as a separate movement. The needle should not be introduced to the hub (the illustrations shown are in error on this point) but should have a margin of at least a half inch to prevent the complete loss of the needle in case of breakage

Aspiration Test to Detect Deep Bleeding—This test is of the greatest importance, especially with insoluble suspensions Its purpose is to detect the entry of a deep blood vessel, for there are a number of large ones in the buttocks with the consequent dangers of delivering the injection mass into the

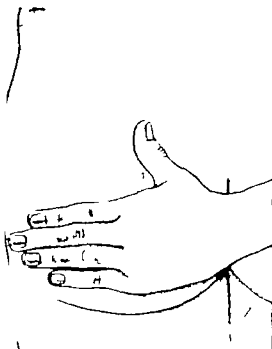


Fig. 184 —Left hand drawing down the buttock.

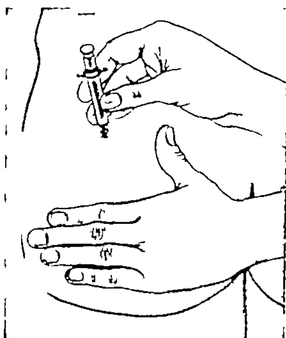


Fig. 185 —Introduction of the needle

blood stream. After the needle has been entered with the right hand, syringe attached (it is not necessary to remove the syringe or to introduce the needle

separately) the left hand releases the drawn-down tissues of the buttock and the right, after accommodating to the new position of the syringe and needle steadies the syringe while the left hand is used to pull upward on the piston, aspirating for a period of not less than five and preferably ten seconds (Fig 128) *No other method seems quite so effective in disclosing leakage of blood in the neighborhood of the needle point.* If the slightest trace of discoloration appears in the suspension within the syringe, the needle is withdrawn and a new entry made 1 or 2 cm distant from the first one At times an operator may enter an unsuspected deep abscess, securing pus or a grumous fluid instead of blood.

Injection.—The introduction of the suspension should not be forced and t should seem rather to flow in. Gradual withdrawal of the needle during in

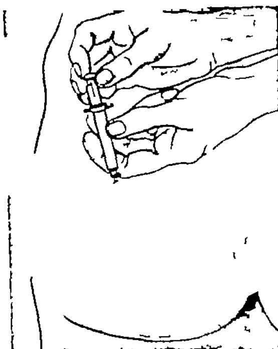


Fig. 128.—Aspiration to test for the presence of the needle in vein.

jection has been recommended but only in the case of larger volumes of solution Injection under pressure and withdrawal both carry the risk of leakage along the needle track with resulting nodular infiltrations of connective tissue and skin. These can be almost entirely avoided by the use of small enough needles and the quick upward push of the downward-drawn superficial tissues as part of the 'valve action secured by the left hand

Old fibrous buttocks, "*fesse en bois*," which have been the recipients of long series of intramuscular injections, sometimes positively refuse to be injected any further and either return the suspension into th needle or through the puncture wound on withdrawal.

Massage.—An extremely important tem following intramuscular injection is *adequate massage* (Fig 129) This point has been emphasized by Boyd and by Colonel Harrison It is well to massage the site of injection

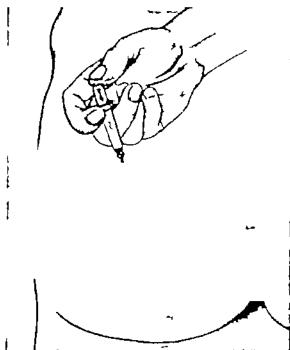


Fig. 127 —Injection the emulsion or solution should flow in freely and not have to be forced



Fig 128.—On release of the left hand the tissues of the buttock return to their normal position, producing valve action. The emulsion is spread out in the muscle tissue and leakage prevented by persistent massage ith cotton pledget. The massage may be prolonged to five minutes or more by the patient.

deeply and firmly though not roughly for at least one minute while the patient still lies on the table, and Colonel Harrison has had very satisfactory results from having the patient massage himself still longer with the use of a species of flat glass pestle for which the doubled fist is only a fair substitute Time spent on careful massage materially favors the absorption of the drug and reduces the incidence of post-injection discomfort.

The prevention and treatment of complications of intramuscular injection are considered in the next chapter (p 305)

THE TECHNIC OF INTRAVENOUS INJECTION

Unlike golf the intravenous injection has no official stance, no professionally authoritative technic of drive and putt. An average degree of proficiency in intravenous work can be acquired with reasonable rapidity pro-



Fig. 109 —Plaster manikin of an arm with venous circulation of rubber tubing, colored water for blood, rubber dam for skin, and yellow solution for injection used to train students in intravenous injection technic.

vided some thought is given to a definite reasoned-out system of movements. That this is seldom undertaken is suggested by the really surprising posturings one occasionally observes through the glass windows of operating and treatment rooms. For purposes of instruction, one of us (J H. S) attempted to detail in 1917 the steps of a technic of intravenous injection which had gradu

ally evolved on his service from a combination of reasoned considerations and the good points of several methods which he had observed and used This technic, assisted by manikins (Fig 129) has since been employed successfully on our University service for student instruction (Stokes and Beerman) Provided the series of steps here described is rigorously followed and exactly repeated the desired result, a successful venipuncture can be obtained in the overwhelming majority of cases The essential items in the correct technical approach involve

1 A satisfactory choice of needle
2 The position of the arm

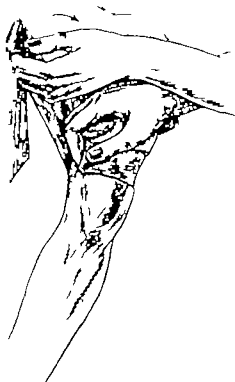


Fig 130.—Method of application of the band tourniquet to the left arm.

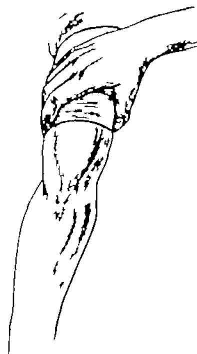


Fig 131 —The band tourniquet, in place, can be held by the patient or assistant, and released simply by loosening the grasp, without jerk or distortion of the veins.

3 A proper application of the tourniquet.
4 The identification and preparation of the vein.
5 The four-point technic of entry

The Needle —This has been discussed on page 288 Due allowance, of course, must be made for the taste of the individual operator in selection. In general, however it may be said that most needles for intravenous work are larger than necessary and cause needless pain and leakage.

The Position of the Arm and Operator —The arm should be extended at right angles to the body with the patient lying down. A sitting position is preferred by some operators, but in each case it is essential that the arm rest

on a slightly slanting support at desk level so adjusted that the elbow is really in a state of forced extension. Much trouble arises from failure to extend the arm completely. It is wisest to expose the entire arm and neck without constriction, the arm being drawn from the sleeve rather than the sleeve being rolled up.

The operator should address himself directly to the arm, working with his line of sight along the course of the vein which he expects to enter and not at even the slightest angle to it. Offside entry is a frequent source of difficulty.

The Tourniquet.—A broad rubber band, such as an Esmarch bandage, a piece 30 inches in length by 2 or 3 inches in width, is the most satisfactory tourniquet, though pieces of rubber tubing clamped by hemostats are frequently employed. When the band tourniquet is used, as in Figs. 150, 151, the folded end may be tucked toward the outer side of the arm and the encircling band drawn over it under tension, thus satisfactorily compressing the arm and catching the end as the band is brought across to the median side. Assistant or patient can then easily control the tourniquet by pressure with the thumb and index finger on opposite sides of the arm, and release without twisting or jar can be secured simply by letting go and lifting the part of the tourniquet covering the anterior surface of the arm. In applying a tourniquet on muscular arms, the compression should not be too great, lest the arterial supply also be partially cut off. The use of the blood-pressure cuff controlled by the patient, also makes a satisfactory but rather more troublesome tourniquet.

Identification and Preparation of the Vein.—The arm should always be inspected before and again after application of the tourniquet. Injection of arsenicals into varicose veins of the leg is deprecated as unnecessary and inadvisable. Palpation may be of more assistance in deciding the vein to use than inspection. Light downward pressure and cross-stroking with the ball of the finger will identify even a very whitewalled or deepseated vein. The poorest types of veins are the pale superficial tracery, easily visible and distensible, but very thin walled; the corded, tortuous or stiff walled veins poorly fixed in a lax, atrophic skin, that recoil and wriggle up the arm before the needle; and outright invisible veins under a deep panniculus. Such veins, inaccessible elsewhere, sometimes appear for 2 or 3 cm. of their length, just at the elbow bend, as a pale blue spot, invisible by very yellow or otherwise poor light but palpable with a "distended tube" feel on downward pressure with a sensitive finger. A skilled operator will often manage a difficult case much more by palpation of such veins than by sight. A watch should be kept for previous thrombosis, which can be recognized because the vein, paler than normal, slips sharply or snaps under the finger as it is drawn across it and yields a definite cordlike feel. Where one arm fails to show a satisfactory vein on first inspection, the other arm should be investigated. Where possible, arms should be used alternately for intravenous work. The point for entering a vein should be as near the operator and as far from the heart as possible, so that if a second puncture becomes necessary, it may be made above the first to avoid leakage of the injected liquid through the original puncture wound.

Poor Veins.—Poorly developed or difficult veins may often be given a satisfactory degree of dilatation by the following devices: (1) Several sharp slaps with the flat of the hand at the site to be injected; (2) by distending the arm vessels by soaking in hot water or applying hot compresses; (3) by the systematic use of daily arm gymnastics; (4) by mopping the surface of the

vein with xylene after the sterilization (5) by the routine "pumping up" of the vein by vigorous opening and clenching of the fist followed by clenching during the period of application of the tourniquet (6) by increasing the slant of the arm.

Toughness of the skin, which makes the entry jerky and tends to transfix the vessel, is chiefly a factor in veins at the wrist and at the condyle of the elbow where the resistance encountered is much greater than at the flexure. Veins on the back of the hand occasionally tempt the operator to his later regret, for the toughness and mobility of the skin the shallowness of the veins, and the delicacy of the walls, all tend to a poor technical result.

Preparation of the Injection Site.—Two per cent iodine in ether or tincture of iodine may be employed for sterilizing especially on dirty arms, but vigorous scrubbing with 70 per cent alcohol as in intramuscular injection until the skin is red serves both to dilate the vein and to provide adequate surface sterilization. Iodine must be avoided in highly susceptible skins or in patients threatened with dermatitis.

Local Anesthesia.—One of the seemingly trivial elements in smooth-running technic is the confidence and cooperation of the patient. Operating under general anesthetic, one seldom realizes the psychic effect on an operator of a nervous or distrustful patient. Panic may seize even the fairly experienced, if the goal is not reached on the first attempt The tense attitude, the arm that bends instead of straightening at the slightest needle-prick, the shrinking way the sounds of remonstrance and disapproval from the patient, are only too efficient in bringing beads of sweat to the operator brow and in damaging the fine movements of the hands on which his success depends. T stop to cool off may only make matters worse, and to fail entirely may damage his nerve in subsequent work as well as that of his patient, more than is realized. For these reasons we have insisted on local anesthesia for years in the use of all needles under 20-gauge, with the most satisfactory results. The simple injection of 1 drop of 4 per cent sterile novocaine solution into the skin with 26-gauge needle forming wheal above the vein at the point of entry transforms intravenous procedure from an affair of haphazard hasty stabs into carefully considered and leisurely maneuver Patients repeatedly attest their preference, and the novocaine solution acts almost instantly so that there is no delay involved in its use. Care must be taken t raise wheal, not to inject into the vein wall or lumen.

The Four-point Entry —Whether an unattached needle or a needle attached to a syringe is employed the four steps for entering a vein are the same.

1 The first step consists in the fixation of the vein with the left hand (Fig 152) This should become absolutely automatic. It is accomplished by drawing downward the skin and tissues of the forearm by the flats of the fingers of the left hand held palm down. Without this step the vein creeps upward with the needle and a miss is very likely to occur

2. In the second step, the needle, whether guided by the fingers or the syringe is entered on the flat in the direction of the long axis of the vein In order to keep the needle as flat as possible, some operators prefer the eccentric syringe nozzle Colonel Harrison advises also that the fingers hold the syringe from above downward, the tips not passing the median plane of the syringe so as to permit it to be laid flat against the arm. We believe that in order to avoid a jerky entry which may traumatize the vein unnecessarily and to make the syringe controllable by the broader bearing surface, the second, third fourth and fifth fingers of the right hand should rest firmly upon the forearm of the patient at the tips, and the movement in introducing the point be thus controlled (Fig 152) In using the Schreiber needle only the fourth and fifth fingers rest on the arm of the patient, the first and second being used with the thumb much as one advances and withdraws the point of a pen in-

stead of using the coarser movements of the forearm. With the bevel of the needle uppermost and with slight downward and forward pressure the point is pushed through the skin but in the first movement is not permitted to enter the vein. This completes the second step (Fig 132)

3 The third step in the four-point entry consists in the puncture of the upper surface of the vein wall. With the point of the needle just visible as a slight elevation under the skin, advance the needle approximately ½ to 1 cm.

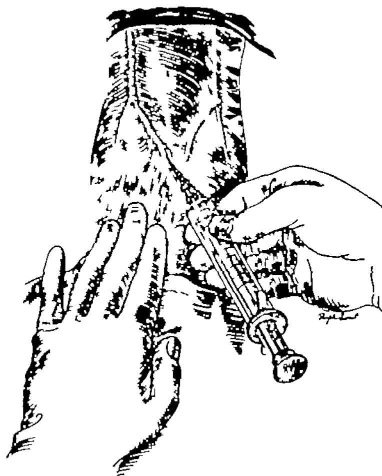


Fig. 132.—Syringe technic First motion, entering the skin, showing the tension exerted by the left hand to fix the vein and the pressure with the right for the purpose of steadying the syringe The needle point is visible under the skin, directly over the vein

so that it is visible as a ridge above the upper surface of the vein wall (Fig 133) Then very slightly raise the butt of the needle or the syringe coincidently with downward pressure of the point upon the roof of the vein. A slight advance of a properly sharpened needle then punctures the vein wall, and the moment this occurs the syringe or needle butt is again dropped toward the forearm flattening the needle out along the long axis of the vein, to prevent puncturing the far side of the vessel. The needle is then pushed up the vein for a distance of approximately 1 cm in order to avoid any possibility of leak

age under the bevel and to avoid discharging an irritant too close to the point of trauma

4 The fourth step is the demonstration of the fact that the needle is completely within the lumen of the vein and entirely free It consists in releasing

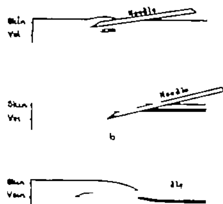


Fig. 133.—Sagittal sections showing the successive positions of the needle in the technic illustrated in Figs. 129–130. *a*, Entering the skin above the vein *b*, angle for entering the vein *c*, advancing the needle after entering.

the tension of the left hand on the forearm of the patient, and while still holding the needle or syringe in position by the right hand resting on the skin of the patient s arm in demonstrating the free flow of blood by pulling backward on the piston of the syringe or witnessing the gush of blood from the hub of

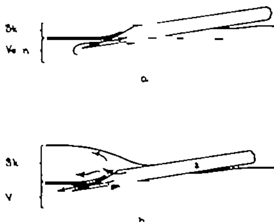


Fig. 134.—Illustrating the effect of partial puncture of vein, with long-beveled needle *a*. Return of blood has been secured without completely entering the vein *b*, infiltration of the subcutaneous tissue even after return of blood has been secured, soon injection is begun

the unattached needle where such is used (Fig 135) The characteristic spurt of the stream of blood across the fluid in the syringe is an absolutely essential concluding test of the correctness of the entry and must always be made before any attempt to inject the syringe contents or other medication is begun Even with a 26-gauge hypodermic needle, it is possible by pulling backward

on the syringe piston to secure a completely satisfactory return of blood, though in smaller amount, demonstrating the freedom of the point in the lumen of the vessel.

Procedure if Free Return of Blood Is Not Obtained.—If after introduction of the needle a free flow of blood cannot be obtained, the following pro-

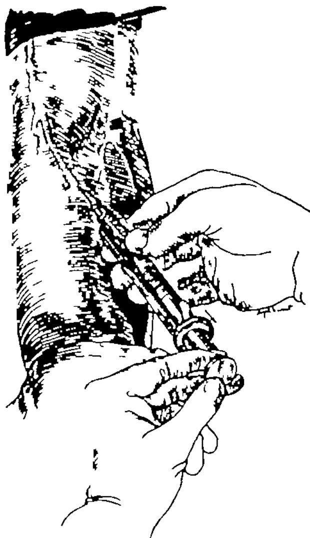


Fig. 185.—Syringe technic. Needle has been advanced, and return flow tested by pulling on piston. A stream of blood should shoot across the fluid if proper entry has been made. The right hand maintains its pressure.

cedures may be tried successively to ascertain the difficulty (1) The patency of the needle should have been investigated before injection by drawing freshly distilled water through it from a small sterile tumbler of water kept for this purpose. In the syringe technic air may be aspirated through the needle into the syringe and again expelled before the injection is given (2) depress the

point of the needle within the vein without advancing: the bevel may be shut off against the top of the vein (3) feel for the needle point with the free hand if it is still above the vein and has not entered the wall, it can be easily felt (4) *the syringe piston may stick and may be loosened by twisting in the barrel* and pulling back (5) transfixing of the needle point on the opposite side of the vein provided the vein has not been completely transfixed, can be remedied by slowly lifting up the needle point while the needle is withdrawn a *short distance it will come away with a quick snap if it is simply caught in*

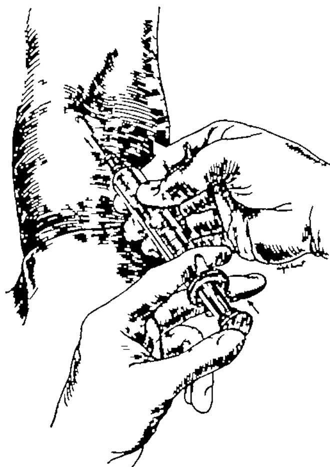


Fig. 126.—Syringe technic. Injection. The guard we have later found may be discarded and the piston controlled better by the thumb and two fingers of the left hand, since no force should be used.

the opposite wall (6) the needle may then be quickly advanced with the point *raised as high as possible, flattening the needle or syringe down to the* surface of the arm as much as possible (7) if the above measures fail the needle may be withdrawn until the point is just short of the skin puncture and another advance made under guidance of the palpating fingers. If this procedure fails twice, the needle should be withdrawn and retested for patency and the point carefully examined while this is being done elevation of the arm with pressure over the vein by a cotton pledget may make it possible to

use the same vein again (8) if leakage of blood into the subcutaneous tissue occurs during venipuncture begin over at another point never attempt to inject through a hematoma (9) never proceed to inject until certain that the needle is in the vein to inject a little and ask the patient if it hurts is evidence of lack of skill (10) one skin puncture may be used for several attempts and every effort should be made to make this one suffice (11) cutting down on the vein is absolutely inexcusable in these days and patients whose veins seem so inaccessible as to suggest the need for such a measure should be sent to an expert (12) make no comments audible to the patient regarding the condition of your needle.

Technic in Children.—The development of satisfactory intramuscular medication has made intravenous injection in infants less important, but it may occasionally be required. If necessary in small child, one or two skilled and determined assistants are usually necessary The child must be wrapped in triangular blanket similar t an intubation blanket, which completely restrains and immobilizes hands and feet. The child is then placed at full length on the table with the head turned t one side and firmly held. The crying of the child will usually distend the jugular vein and an entry can easily be made ith small very sharp steel hypodermic needle attached to 5 or 10 cc. syringe. Larger syringes are too hard t control. If head vein is used, such as the anterior auricular an all-glass hypodermic syringe may be employed Injection into the superior longitudinal sinus is mentioned only to be condemned, for serious reactions have occurred.

Older children, if visible arm veins appear may receive neoarsphenamine t the start with syringe and 26-gauge hypodermic needle until the child' confidence is gained. If arsphenamine (606) is to be used, the ordinary 20-gauge needle may be introduced by the syringe technic the syringe detached and the adapter on the container tubing inserted, if the dose is too large to use 20 cc. syringe. The 20-gauge needle should not be used without local anesthesia on child' arm, for once the confidence of a husky child is lost. battle royal usually ends in an infiltrated arm and the defeat of the operator Parents should not, in general, be admitted to the treatment room with their children. The repeated occurrence of uproar from children under treatment is evidence that the staff is working below par

Rate of Injection in Intravenous Technic.—This is controlled in accordance with the methods and according to the standards outlined on page 260 In general arsenicals should be administered intravenously at a slow rate, but mapharsen produces less trouble when the rate of administration is rapid.

TECHNIC OF INTRAVENOUS DRIP

The following description is abstracted from the account by Leifer (1940) given at the conference on massive arsenotherapy in early syphilis by the continuous intravenous drip method in behalf of the Committee on Massive Drip Intravenous Therapy See also Treatment of Early Syphilis, Chapter XIV

The apparatus employed in the intravenous drip is packed and autoclaved in special container with slot containing perforations hich is open while in the autoclave and closed at all other times to prevent contamination. Each set consists of gravity flask and two lengths of transparent rubber tubing connected by Murphy drip. The longer tubing is attached to the gravity flask; the shorter to an adapter which fits standard 20-gauge 1.5 inch needle. The drugs are dissolved in solution of triple distilled water containing 5 per cent dextrose The content of an ampule containing 60 mg. of mapharsen is dissolved in 600 cc. of the diluent (Vacoliter equipment may be used). Four doses of the drug in the diluent are given without intermission each day so that each patient receives 240 mg. of mapharsen in 2400 cc of 5 per cent dextrose solution which contains 120 grams of the sugar The rate of flow is approximately 6 cc. minute. Ordinarily the drip is set up about 8 m and the full dose has been injected by the end of ten to twelve hours. At the end of this period the needle is withdra n, treatment being discontinued during the night but resumed the next morning The procedure is carried out daily for five con-

secutive days until total of 1200 mg of the drug has been administered in 12,000 cc. of diluent containing 600 Gm. of dextrose. The total arsenic content is approximately 360 mg.

The choice of the vein is an important consideration. The elected site for the insertion of the needle has been a vein in the forearm between the elbow and wrist. This permits free movement of the elbow and no splint is required. The patient may assist in feeding and in nursing procedures such as the use of the bed-pan. There is less danger of dislodging the needle from this site than at the bend of the elbow where motion occurs. It is desirable to insert the full length of the needle up t the hub for firmer anchorage. The right and the left arm are used alternately for the injection procedure. Usually vein can be employed again after rest of twenty-four hours. Fresh solution is prepared for each patient t the end of two to three hours, and the gravity flask refilled. Meals are served on the ordinary bed trays. Patients can feed themselves. They are also capable of handling the urinal, and may read, listen to the radio, or play cards during the day Disturbance by the use of the bed pan may be prevented by having the patient evacuat or have an enema during the evening when treatment has been discontinued. After discontinuance of therapy in the evening the patient may get out of bed. They suffer little or no discomfort and may register gain in weight.

TECHNIC OF SPINAL PUNCTURE (RACHIOCENTESIS)

The ill-performed spinal puncture plays directly into the hands of neurosyphilis first by providing a specimen unfitted for complete examination (blood cell contamination) and secondly by leading the patient to break treatment or refuse further spinal fluid control. Unfortunately the examination of the spinal fluid is a much less simple procedure technically than the mere drawing of blood for a serological test. Lumbar puncture the simplest of the methods employed for obtaining the fluid presents a considerable technical difficulty quite measurable discomfort for the patient in the form of possible reaction, and a distinct though slight element of risk of injury or even of loss of life It follows, therefore, that except under pressure of emergency it should not be attempted by the inexperienced or without proper control over the patient. To do the test in the office, with the patient sitting on a stool or table, is distinctly second-best procedure. In certain circumstances, however it is unavoidable and we have seen no striking disadvantages, if the patient is cooperative With sufficiently small needles, an uneventful puncture and the proper use of sedatives a satisfactory ambulatory technic has been developed.

Equipment for Spinal Puncture.—As in the intravenous technic, perfection in performance is facilitated by uniform and satisfactory surroundings and equipment. The test can be performed at the bedside by an operator of experience On the ordinary low bed the operator should sit on the floor so as to bring the site of puncture a little below the level of the eye Under operating room conditions, a rigid table of such a height as to bring the middle of the back to the level of the operator s chin when seated should be used. If the patient sits, which is advocated only in rare instances of obesity or other special conditions, the stool should be high and the site of puncture also at the level of the operator s chin.

Needles should be sterilized by boiling for ten minutes ith the stylets each rapped with its own needle in thin gauze Alcohol free from corrosives is to be aspirated or poured through the needle before boiling if oil has been used. Additional equipment as follows: (1) One all-glass syringe (2 cc.) and hypodermic needle (26-gauge) for local anesthesia. (2) Two t 4 per cent novocaine, sterilized by boiling. (3) Full-strength tincture of iodine or 2 per cent iodine in ether (4) Medicated alcohol (no corrosives) (5) Six inch gauze squares, sterile gauze sponges, sterile adhesive plaster

A good office kit includes

1 A 8 x 8-inch box containing:
  Three 5 cc sterile corked and labeled test tubes for collecting fluid.
  2 tubes of 4 per cent novocaine solution.
  1 tube sterile distilled water for hypodermics.
  1 tube of codeine hypodermic tablets, or capsules of sodium amytal if this drug is used
  1 tube tincture of green soap
  2 large cotton-wound applicators for applying iodine
  1 hand brush boiled and wrapped in sterile towel.
  Adhesive bandage scissors.
  Medicated alcohol (no corrosives).
  Medicine glass, with cotton for holding tubes.
2. Sterile gown with sterile towel for scrubbed hands.
3. Two pairs dry sterile rubber gloves with powder sponges.
4. Sterile packs containing as used: (a) Towel for protection of bed; (b) large table cover; (c) spinal puncture sheet (8-inch hole) sufficiently large to cover back and side of patient (d) four large gauze dressings ( ) six small gauze sponges

Fig. 137

CONTRAINDICATIONS TO THE SPINAL TEST

1 Old age, especially when accompanied by marked arteriosclerosis. The need for spinal tests in patients over sixty should be carefully weighed.
2. Presence of systemic conditions likely to produce marked lowering of general resistance, as, for example, carcinomatous and other cachexias, threatened or actual uremia, severe diabetes, advanced cardiac decompensation.
3. Any vascular or blood condition likely to result in persistent hemorrhage, such as hemophilia, increased coagulation time from other causes (jaundice, etc.) severe purpura, etc.
4. Intercurrent acute infections, especially of the respiratory tract, ear nose, and throat, and systemic disease in which bacteremia is known to exist, as in pneumonia, typhoid fever early meningococcic septicemia, streptococcal septicemia, etc. There is danger of transfer of the infection through the choroid plexus to the meninges and fluid.
5 Florid untreated generalized syphilis in the spirochetemic stage. Such patients should receive preliminary arsphenamin sterilization (1 or 2 injections)
6. Intracranial pressure, especially when associated with cerebellar symptoms or signs of brain tumor An examination of the fundus of the eye is essential (choked disk)
7 Rare cases of rapidly progressive mental or lower cord tabes.
8. Areas of infection of tissues in the needle path, as, for example, lumbar Pott disease with abscess formation of unknown extent, et
9. Obvious deformity of the lumbar spine which would make entry impossible.
10. Pregnancy

5 White enamel-covered tray containing (a) Two spinal needles with stylets removed and kept with their respective needles by wrapping points in cotton; (b) two 2-cc. all-glass syringes with three 20-gauge hypodermic needles ( ) hemostat for handling needles and so forth.
The contents of this tray should be laid between gauze, the hemostat on top of gauze and boiled in distilled water for ten minutes. The cover of the tray should not be removed, either during boiling or when draining.
6. Mercury manometer if operator uses one
7 Thermometer

Contraindications to Spinal Puncture.—These are summarized in Fig 137 since their preliminary consideration is an essential part of the technic.

Asepsis.—We regard spinal puncture as an invasion of the meninges in which a blunder in asepsis or technic may have the most disastrous consequences because of the inaccessibility of the parts and the low resistance of the tissues affected. We shall describe and illustrate therefore essentially a surgical technic of approach

Fig 138.

IMPORTANT POINTS IN SPINAL PUNCTURE TECHNIC

1. Know of contraindications before, not after. Take temperature.
2. Lumbar puncture presented here as the preferred method. Patient lying on side preferred.
3. With proper selection of needle, use of local anesthesia, and intelligent handling of patient, lumbar puncture is practically and often absolutely painless.
4. Preparation
   - ( ) Mild saline night before. Light meal.
   - (b) Thirty grains bromide or 3 grains sodium amytal night before if nervous.
   - ( ) Codeine hypodermic 1 grain, one-half hour before or 2 t 3 grains sodium amytal.
5. Talk to the patient: tell him t expect (1) local pinprick anesthetic; (2) ten t twenty seconds' toothache-like sensation, often absent, (3) twinge or shocklike sensation in the leg (1 in 4 t 10 cases)
6. Tell him further: (1) to relax, not try t help (2) t let the nurse double him up until chin and knees almost touch (3) not t straighten if hurt or spoken to.
7. For the operator
   - ( ) Skin sterilization with iodine removed by alcohol afterward.
   - (b) Use the fourth or fifth lumbar interspace (crest of ilium landmark), entering at the junction of the middle and caudal thirds.
   - ( ) Use 4 per cent novocaine if no idiosyncrasy
   - (d) Infiltrate skin and dorsal ligament.
   - ( ) Insist on perfect vertical plane for pelvis and shoulders coincidently W tch upper shoulder especially (Figs. 139 140)
   - (f) Handle only the hub of the sterile needle and stylet.
   - (g) Be sure the needle is entered horizontally stylet held in.
   - (h) Guard it with the left hand (Fig. 142)
   - ( ) Make no stabs or uncontrolled movements.
   - (j) Don't attempt t push past or around bone
   - (k) "Drill" if tissue (not bone) is tough. Don't force the needle
   - (l) Take new direction, but not a new puncture of the skin, by partial withdrawal (through the ligament) if necessary
   - (m) If marked pain occurs or blood appears, begin over. After blood use fresh needle
   - ( ) Don't overpass the canal. Learn t know the "feel" of entering. There is risk of hemorrhage in overpassing.
   - (o) Don't ream the puncture. If fluid is slow slight rotation of needle and having patient count may help.
   - (p) Never aspirate
   - (q) Not pressure.
8. The specimen
   - (a) Collect fluid not faster than drop second. Slower preferred. Control by stylet in needle hub
   - (b) Let 20 drops escape before collecting.
   - ( ) Three tubes, numbered seriatim.
   - (d) Total 8 t 10 cc
   - ( ) Cell count from Tube 3.
   - (f) Blood cells repeatedly present (microscopical) mark the amateur
   - (g) Not physical properties.
9. After-care
   - ( ) Warn of needle withdrawal.
   - (b) Have patient roll onto face
   - (c) One hour rest if ambulatory. Four t six hours if in bed
   - (d) If blood appeared, keep in bed t enty-four hours.
   - ( ) If possible routinely twenty-four t forty-eight hours rest in bed, little movement and conversation as possible
   - (f) Warn t report leg or bladder symptoms.
   - (g) Warn of headache treatment.
   - (h) Warn against rough travel for forty-eight hours.
   - ( ) See before final discharge
   - (j) Scott (thesis) and Ills (1941) have reported sedative unnecessary nd active movement or even light ork desirable immediately after puncture

THE ILL-PERFORMED SPINAL PUNCTURE PLAYS INTO THE HANDS OF NEUROSYPHILIS

Technical Considerations.—In Fig. 138 there is presented a summary of the technical considerations involved in spinal puncture illustrated by Figs. 139–142 inclusive. In reminiscences covering now some thousands of lumbar punctures, we would wish to impress, first, the importance of rapport between patient and operator We do not believe that with any except the best trained patient the physician should attempt spinal puncture unassisted. There is great danger in attempting any form of spinal manipulation on uncooperative patients without proper assistance and it is safety first to have someone hold every patient's neck and knees during the puncture.

After seating himself the operator should address the patient before making a move. Most patients have a justifiable anxiety about the test. This is greatly reduced by sodium amytal. The spinal column seems a peculiarly



Fig 139.—Patient lying on the right side, incorrect posture. Note that the upper shoulder has dropped forward and the plane of the shoulders and pelvis is no longer vertical. The twist of the spinal column in this position may make entry difficult or impossible.

vital structure to the average man or woman. The unfortunate term "puncture" reminding one of a collapsed tire, creates a disconcerting impression and should not be used toward patients, "test" being used instead The operator explains that a local anesthetic will be used, that the discomfort, which is slight, will consist, first, of the pinprick of the hypo needle a slight burning sensation, sometimes a feeling described as resembling a toothache for ten seconds, and perhaps, in occasional cases, a jar or slight electric shock in the leg, if the needle touches a "cord" (filament of the cauda) A skillful operator anesthetizing the ligament as well as the skin, can perform puncture after puncture without the patients even being aware that anything has been done The preparation of the patient by warning him exactly as to what is coming, and cautioning him to hold still is of the greatest possible value, not only in preventing accidents but in getting the patient into an attitude of confidence

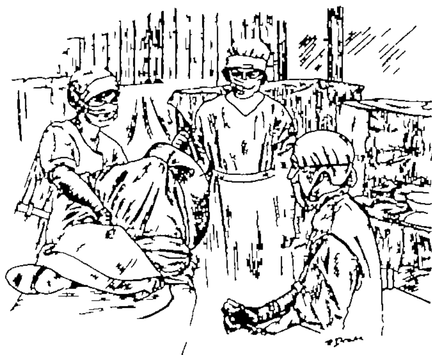


Fig 140.—Correct posture, shoulders and pelvis in the same vertical plane. Note that an assistant holds the neck and knees t prevent unexpected straightening of the back after the needle is introduced.

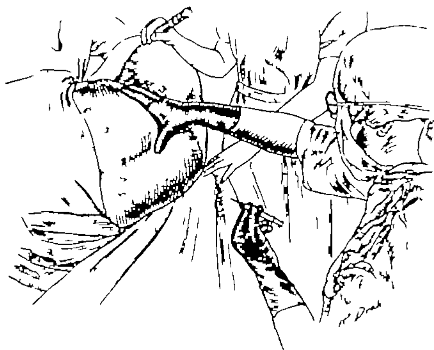


Fig 141.—Establishing the position of the fourth interspace using the iliac crest as guide The back has been painted with iodine. A sterile sheet ith small opening may be used

in the operator indifference to the test and willingness to submit to it again, whenever necessary in the future. The impression made by the first test, if poorly done may absolutely preclude a second.

Entry of the Canal.—This should in general be made between the third and fourth or the fourth and fifth lumbar vertebrae In some cases it may be made between the fifth lumbar and first sacral, or between the second and third lumbar but never above the second lumbar vertebra. The line joining the crest of the ilia passes across the spinous process of the fourth lumbar vertebra. Careful palpation is an invaluable preliminary With the Greene type of point, the skin and ligament may be "drilled" by rotating the spinal needle. The puncture of the dura is marked by a sudden loss of the sense of resistance which can only be learned by experience With the blunter types of



Fig. 144.—Introducing the needle bet een the t fingers of the left hand, with the right hand resting upon the left wrist as guide and guard against sudden movements or excessive pressure which may break the needle

needles this is less marked than with the sharper When this "dropping-off place" is reached the operator should go no farther but rem ve the stylet and if the needle point i in the canal fluid will appear almost at once

Management of Immediate Complications of Lumbar Puncture.—Those complications which must be met by the operator on the spot include

1 **Inability to Enter the Canal.**—Consider the possibility of bony deformity hypertrophic spondylitis, trauma, sacralization of the fifth lumbar vertebra, tc. Note whether the bowing of the back is sufficient, and have the attendant increase it *after withdrawing the needle point to the skin level.* Be sure sacrum and shoulders are in a vertical plane. Aim lower or move the needle to another part of the interspace and change direction keeping needle in the same puncture wound and moving the skin about. As a last resort, enter another interspace after reanesthetizing Keep cool and silent.

2 **Inability to Obtain Fluid After the Canal Seems to Have Been Entered.**—True "dry taps" must be excessively rare in fact, though common in amateur experience Most dry taps are technical failures. If you believe yourself in the canal withdraw the stylet. If there is no result when you believe yourself in the canal withdraw the needle slowly taking out the stylet from time to time, or even leaving it out for a short distance You may have over passed If there is no result, re-estimate your distance, replace the stylet, and go a little farther in. Never advance a needle with the stylet out. If this fails, take it for granted you are not in the canal and proceed as with (1)

Slow Drip, Clear Fluid.—If a slight push or pull on the needle will not increase the flow be patient and wait. The slower the flow the better for the patient. It is inadvisable to rotate the needle under such circumstances, unless absolutely unavoidable since it may inflict additional trauma on the dura. Having the patient count, or engaging him in conversation (caution) or having him take deep breaths hastens the flow Pressure made by the thumbs over the jugular veins will also do so.

Fig. 143.

CROSS-ROADS CLINIC LUMBAR PUNCTURE

1 Careful exclusion of ineligibles (age arteriosclerosis, et).
2. Privacy—room cleared.
3. Work concentrated t single session.
4 Experienced operator or visiting team.
5. Stool or chair technic patient sitting.
6. One assistant to hold patient, handle tubes.
7 N prel minary sedative no warnings or instructions.
8. Local nesthesia not necessary but preferred.
9 Asepsis, scrubbed hands, no gloves or gown.
10. Care bout
 ( ) Discarding first 20 drops.
 (b) Labeling tubes on spot, no mix-ups.
 ( ) Prompt transfer t laboratory and adequat handling and examination.
11. After test, patient stands up, dresses, walks out, told may do light work, report and lie dow if headache or leg pain.

Gush of Fluid.—The normal flow of fluid from a successful puncture varies with the needle and the position in the canal, but seldom exceeds 70 drops per minute If the fluid shoots out in a stream or gushes in a rill, immediately *reinsert the stylet or cover the opening with the finger since sudden release* of pressure may be serious. Control by keeping the tip of the stylet in the opening and draw *very slowly* and not in excess of 3 to 5 cc

Blood-tinged Fluid.—A fluid which is visibly tinged with blood is unsuited for a cell count. The sources of blood are (1) ill fitting stylet (2) removing stylet too often to see if canal has been entered (3) moving needle back and forth with stylet out (4) needle point in a vein (5) trauma to the venous plexuses of the dura which permits blood to enter the canal (6) blood from hemorrhage into the canal at a d tance, a from cerebral injuries, trauma, apoplexy etc

Traces of blood when the fluid first begins to flow are evidence of technical error Gross blood contamination necessitates a repetition of the puncture at a higher level and at once *Use a fresh needle* A steady flow of bloody fluid means injury to a vein or venous sinu and further attempt to get a clear

fluid are for the time being useless Blood even microscopical, is usually one of the earmarks of the inexpert operator Overpassing entering the plexus against the vertebral body and removing the stylet too soon or too often are the commonest sources of this difficulty

When a fluid has shown definite evidence of blood contamination it is especially important that the patient be kept absolutely quiet in bed under observation with an ice-cap to the spine for at least forty-eight hours

Collection of the Specimen.—*Allow the first 30 drops of a clear fluid to escape in order to remove the last traces of slight but inevitable blood contamination from the needle* The specimen is then collected in three 5-cc. tubes which, if not immediately removed to the laboratory must be corked with sterile corks (not gauze or cotton) In all other particulars the specimen must be handled exactly as a specimen of blood for serological test. The three tubes are numbered serially and the third is used for the cell count. The total amount of fluid removed should range from 8 to 10 cc., if all tests are to be done. Some observers feel that if the manometer pressure of the fluid exceeds 20 mm. of mercury there is risk of medullary block if spinal fluid is removed for diagnosis. Normal manometer readings range from 6 to 20 mm. Hg or 40 to 200 mm. water A sudden spurt of fluid is certainly a warning, but pressure estimates from needle flow are untrustworthy for the slighter variations are influenced by bore and position of the needle and placement in the cavity or concealed obstruction. Careful note should be made of physical properties, color turbidity and coagulation of the fluid, if it occurs. Fluid flow can be absolutely controlled by the tip of the stylet in the opening of the needle.

The nonoperative complications of spinal puncture are considered in the next chapter

TECHNIC OF CISTERN PUNCTURE

Cistern puncture performed by Obregia in 1908 but standardized and developed by Dixon, Weed, Ayer and others, and performed in this country by Ayer and his associates in 1919 is at the present time the subject of enthusiastic advocacy by Spiegel, Mennenheimer and Jacobi. Spiegel and Jacobi speak of the "fear complex" which still justifiably interferes with the wholesale popularization of the procedure In spite of repeated and enthusiastic endorsement of cisternal puncture by competent men (Kulchar (1940) Franks (1940), Alexander Fox and Schoch (1943)) it is not t be commended t practitioners and is limited at this time to its applicability to those who can take training for it on the cadaver and use it under controllable conditions. Cistern puncture is claimed to have many advantages, including relative painlessness, freedom from postpuncture reactions, including headache, and relative indifference of the patient to the procedure, which permits its indefinite repetition (Mennenheimer) Spiegel claims that with perfected technic bloody fluids are rarely met with and relatively large amounts of fluid may be withdrawn with no after-effects.

The dangers of cistern puncture, particularly by the direct, or original Ayer technic, consist, of course, in overpassing with injury to the medullary structure and hemorrhage from the dural plexus. The depth of the cistern at the point of puncture is pproximately 1 t 1½ cm., which allows somewhat greater margin than in the lumbar region; modified however by the presence of the medulla itself rather than the relatively much less easily injured cauda equina.

Two technics of cistern puncture exist, the direct technic of Ayer[*] using as the line of entry along which the needle is directed, an imaginary line joining the glabella and the midpoint of the external auditory meatus. American advocates of cistern puncture now commend, however the indirect technic of Eskuchen, performed with needle carrying stop, as devised by Spiegel Spiegel has adopted over period of years combination of the direct and indirect methods because it is impossible to fortell before puncturing the dura whether one will be able t touch the posterior edge of the foramen magnum of the occipital bone.

In the performance of the Eskuchen puncture, the patient may sit, or lie on one side, the

* This is the technic as described by Jacob.

landmarks being clearer in the sitting position and flow of fluid only being obtained in the lying position which may be carried through without assistance (Spiegel, personal communication, 1943, prefers to have the patient in the lying position. In the sitting position one does not always know when the dura has been punctured, as no fluid will flow on puncture. This necessitates the use of a syringe thus adding another hazard since the needle may be moved in attaching the syringe). The head is moderately flexed on a small, hard pillow which must be high enough to impart to the cervical spine a perfectly horizontal position. The head must be, moreover in a perfect front-to-back plane and not turned to one side or the other The important external landmarks are the occipital protuberance, the spinous process of the axis or second vertebra, and the deepest depression at the back of the neck. Placing the left index finger on the external occipital protuberance, the operator palpates downward in the middle line closely hugging the occiput, until the fingertip reaches the deepest depression. Immediately behind this spot will usually be found the spine of the axis, which is the first essential bony landmark. About ½ cm. above it the needle is inserted, pointing in the approximate direction of the outer end of the eyebrow

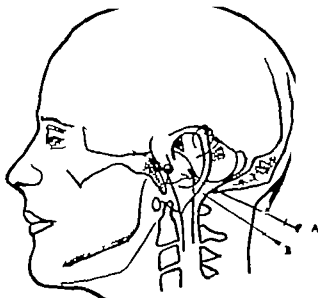


Fig. 144.—Sagittal section of head showing anatomical relations involved in cisterna puncture. (Courtesy of Dr Leo Spiegel.)

From this point on, no definite landmarks are given by Eskuchen. Advancing the needle along the line thus indicated (toward the eyebrow) the point first encounters a bony obstacle *which is the squamous portion of the occiput. The needle handle is then lifted repeatedly and* slightly the point being advanced by successive movements along the edge of the bone to the exact spot at which the point slips off the bone and meets the elastic resistance of the ligament covering the atlanto-occipital membrane. *If the needle point at first introduction falls below the* occiput, it may by depressing the handle, be directed upward until the bony landmark *is found.*

When the needle point slips off the occipital bone the operator removes the stylet and again advances very slowly and cautiously for a distance varying from ½ to 1½ cm., the latter marking the outer limit of safety A few millimeters is usually enough. A feeling of a dropping-off place may be absent, which makes the removal of the stylet the more important. The amount of fluid removed and so forth are identical with those in lumbar puncture.

Mennsenheimer in an examination of 10,000 punctures, found reports of 7 fatalities, most of them in the early history of the procedure. The list of minor mishaps given by Jacobi is important enough to deserve separate study and his article together with the writings of Spiegel, is commended to those who desire to study the technic on the cadaver in preparation for its use on patients.

TECHNIC OF INTRASPINAL MEDICATION

The details of intraspinal therapy are fully discussed in the first edition of this work, pp. 209–214 and 260–273. The reduction of this procedure to relatively minor importance with the advent of tryparsamide and malarial therapy justifies only condensed description of the Swift Ellis procedure at this point.

The Preliminary Intravenous Injection.—The patient is given intravenously an injection of the arsphenamine which has been adopted for his treatment, the dose ranging from one-half to two-thirds the adult weight maximum. At an interval ranging from ten to sixty minutes, and usually forty minutes after this injection, 30 cc. of blood is drawn from the cubital vein through large needle into each of two large sterile centrifuge tubes. This blood is allowed to stand for one hour at room temperature and the clot is then separated under aseptic precautions from the sides of the tube with sterile knitting needle. It is then placed in the ice-box and allowed to cool and shrink, which affords larger yield of clear serum. Both serum and clot are then centrifuged



Fig. 145.—"Second pipetting" in the Swift Ellis intraspinal technic. After the serum has been separated from the clot by the first centrifuging, it is pipetted off ("first pipetting") and recentrifuged at high speed to throw down the last traces of red blood cells. Special care must be taken to avoid aspirating blood cells into the second pipetting, so that an excess of serum above the amount required for treatment is essential.

in high-speed centrifuge at 2000 revolutions, for ten minutes. It is extremely important that each tube be properly balanced by weight against similar tube containing water since at the speed the centrifuge is run, serious damage to the bearings and possible wrecking of an improperly balanced tube follows neglect of this precaution. The strictest asepsis must be maintained throughout this and subsequent manipulations.

After the first centrifuging, the supernatant serum is pipetted off with 25 cc. pipet (Fig. 145) into similar centrifuge tube and centrifuged again at the same speed for fifteen minutes to throw down the last of the red blood cells, which are responsible for marked irritative symptoms in the spinal canal. A second pipetting off of 25 cc. of the serum is then done, care being taken not to draw off the serum within ½ inch of the bottom of the tube from the second centrifuging. This tube of double centrifuged serum is then placed in the ice-box over night. At this point the Ogilvie arsphenamine reinforcement may be practiced, if desired. If the Swift-Ellis technic is followed, the serum (45 cc.) is placed in the warming oven at 56 C. for seventy minutes. The

entire procedure, including the introduction of the serum into the spinal canal, may be completed in one day after the technic proposed by Kolmer the intravenous injection being given in the morning and the intraspinal treatment in the afternoon.

The technic of introduction of fluid into the canal calls for the equipment shown in Fig. 146, the needle being introduced as in lumbar puncture. The buret with tubing and adapter is attached to the needle after free flow of fluid is obtained, and 30 cc. allowed t collect in the buret. The tube is pinched repeatedly during this process to allow contained air t escape into the container The specimen for spinal fluid examination is obtained from this fluid and the remainder discarded The emptied buret is then allowed t fill once more with from 20 to 40 cc. of fluid, depending on the patient, and t this fluid the 25 cc. of auto-arsphenaminized patient serum is carefully added, good mixture being secured. By raising the buret container above the level of the needle, the mixture slowly flows back into the canal. The container is then disconnected and the needle withdrawn, as in spinal puncture.

As soon as the treatment is completed, the patient is rolled over on his face and the after care is that of spinal puncture (see p. 320) except for the closer watch kept for complications and the palliative relief of leg pains, if they occur

In the effort to treat the base of the brain and the pathologic condition of primary optic atrophy it is essential to carry the fluid introduced in the lumbar region, higher up the canal This may be done by the Gennerich double puncture technic, in which two punctures are made,

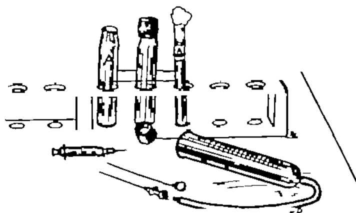


Fig 146—Equipment for administration of intraspinal arsphenaminized serum. The graduated buret has capacity of 40 t 75 cc A specimen of spinal fluid is collected before introducing the serum.

one between the second and third and the second between the fourth and fifth lumbar vertebrae, following the usual technic T enty-five cc. of fluid is allowed t flow int the upper buret and as much additional into the lower can be collected. During this process the head should be high and the pelvis low As much fluid as possible should be drawn into the lower container Most of the fluid in the upper container is discarded, the Swift Ellis serum is added, the fluid is allowed to flow in, while the lower container is held in reserve. The head of the patient is then lowered and the buttocks elev ted and the contents of the lower container (caudal) is allowed to flow in, carrying the previously introduced arsphenaminized serum up the canal toward the base of the brain. That the purpose is accomplished is attested by the fact that there are no lower-cord symptoms following the treatment but that posttreatment pains may appear in the arm and about the waist together with dull headache.

Intracisternal treatment may be given by the Swift Ellis technic in preference t the Gennerich procedure and the patient may also simply be more or less stood on his head after the ordinary lumbar Swift Ellis treatment in the effort to secure upper-cord and basilar effect.

The complications of intraspinal medication include pains in the legs, sharp and knifelike suggesting those of tabes dorsalis; and evidence of irritation of the sexual and bladder centers of the cord. Aspirin and codeine may be used for relief Fever is an unusual occurrence, headache is much less common than after spinal test alone. Significant cord irritation includes the development of saddle anesthesia, which may be transient or permanent, and retention of urine sometimes not complained of by the patient for number of hours or longer The previously existing

Fig. 147

COLLECTING AND HANDLING THE BLOOD SPECIMEN FOR THE WASSERMANN TEST

1. Blood is usually drawn from the cubital vein in the bend of the elbow. In order to distend the vein with blood, tourniquet must be pplied to the arm to stop the venous return.
2. Procedure should be aseptic throughout. Specially prepared tubes are used, supplied by the laboratory and usually sterilized.
3. Syringes and needles used in drawing the blood must be boiled for five minutes in clean water. Chemical disinfectants or alcohol must never be used.
4. The skin is disinfected with alcohol or iodine. Do not use agents which leave prolonged stain.
5. Timid patients or those who may faint should lie down before the test. This is the better practice in all cases.
6. Not less than 5, and better 8 or 10 cc. of blood are necessary for the examination. Some Wassermann tests can, however be performed on as little as 1 cc.
7. In drawing blood with the syringe remember to work quickly for it will coagulate and ruin the syringe. Expel it at once into the tube provided by the laboratory and pull the plunger from the syringe barrel.
8. Keep the tube cont ining the blood right side up: cork it at once and label it. There is no worse crime in nursing than t mislabel or mix up bloods for Wassermann tests. You may pin a diagnosis of syphilis on to the wrong person. Observe the following precautions:
   (a) Paste one of two perforated gummed labels attached to each other to the laboratory sheet.
   (b) Fill them out in duplicate in ink or indelible pencil ith name of patient, date and physician to whom report is to be made.
   (c) Draw the patient blood and expel into the tube, and *then and there*, before separating patient and blood, cork the tube, separate the duplicat perforated label, above mentioned, from its fellow glued t the report slip, and past the duplicat on the tube of blood, fastening it still more securely by rubber band.
   (d) Then, and only then, may blood specimen and patient be separated.
   ( ) Never draw another specimen until the first is completely disposed of.
   (f) Mistakes begin when patient and blood are separated before labeling, and label and report slip are not automatically duplicated.
9. Allow the tube t stand t room temperature for fifteen or twenty minutes. This will give time for clotting. Do not tip the specimen around in the tube.
10. Bloods hich are not delivered to the laboratory t once must be kept in the ice-box from the time clotting occurs.
11. Bloods should be delivered to the laboratory t the earliest possible moment so that they may be centrifuged and inactivated.
12. Handle tubes with the greatest care. They have trick of slipping through the fingers and striking hard objects, and a blood specimen once lost may never be replaceable.
13. Report any breakage at once. Never set tubes dow in glass tumblers or other containers without having something soft like cotton on the bottom.
14. Do not try to carry a number of tubes simply by putting a rubber band around them. Always hold one hand under them.
15. Never deposit blood specimens t random anywhere including the laboratory. Have definite place for them, preferably in the ice-box. Never lay them down on a table at room temperature or give them t some by-stander unless specifically instructed.
16. Blood may in early cases be infectious. Wash it t once from your hands. Do not spill it around, and if you splinter test tube, report yourself t once t physician t be sure that you have not been infected by cuts or minute particles driven into the skin. Pricks from needles used in drawing blood are even more serious. Report them t once.
17. Blood which spurts into the mouth or strikes the face or eyes is serious and you should report yourself at once.
18. Blood specimens from infants may be obtained from the infant or maternal end of the umbilical cord at birth. I older babies stab in the heel ith small trocar will, with some effort, yield enough blood for single stage test. The jugular vein can be entered ith small needle and syringe ith proper assistance t hold the head. Entering the superior longitudinal sinus is done but not recommended. Most children have elbow veins accessible to competent operators.

lower-cord symptoms are sometimes accentuated and myelitic symptoms appear in rare cases. Intercurrent infections may complicate the picture and patients should be warned of exposure after intraspinal treatment. Meningeal infection occurred once in our experience in 8000 injections. The mortality in our experience was two in 8000 treatments.

COLLECTING AND HANDLING THE SPECIMEN FOR BLOOD SEROLOGICAL TEST

The instructions summarized in Fig 147 were developed for nurses but they have proved useful enough in instructing medical students to justify their introduction here. The one-man technic illustrated in Figs. 148–151 inclusive can be used in dispensaries and crowded services. The needle used is the 16-gauge or a 20-gauge large antitoxin needle to which a 4-inch piece of



Fig 148.—Applying the tourniquet (rubber bandage) in one-man Wassermann technic, sitting. The ends of the bandage are crossed on the front of the arm under tension, twisted upon each other and the patient seizes the twist between thumb and index-finger of the right hand The fist of the left hand is firmly pressed against the operator's knee. At the conclusion of the blood drawing the patient simply releases the "twist" and, as the tourniquet drops off, presses his thumb upon the cotton pledget covering the puncture (Fig 150)

rubber catheter has been attached The Kolmer modification of the Keidel tube (Fig. 168) is supplied by most private laboratories with proper mailing containers. The tourniquet is applied as in Figs. 150 151 The arm must be fully extended and the closed fist tightly pressed against the operator's knee or hip if standing The patient releases his own tourniquet when the specimen is obtained and presses the thumb of his free hand on the pledget as it is placed over the needle.

Collection of Blood Specimen from Infants.—A fair yield of blood which should not be less than 1 and preferably 2 or 3 cc may be obtained from infants or persons with difficult veins by constricting a finger or the great toe and making a deep puncture with a bloodletting stylet or an acne lance The blood can be collected with an eye-dropper (previously sterilized) and dis-

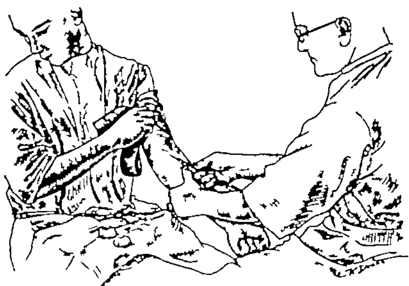


Fig. 149.—One-man Wassermann blood-drawing technic. Traction with the left thumb fixes the vein, and syringe or tube is held in the right hand as in the syringe technic of injection. The patient presses his fist against the operator knee and releases his own tourniquet. A similar technic may be used with the patient lying down



Fig. 150.—Pressure with sponge over the needle as the latter is withdrawn prevents bleeding. The patient continues the pressure on the sponge with his thumb.

charged quickly into a small test tube standing in a tumbler A Wright capsule which consists of a bulb drawn into a capillary tube at both ends, one end being curled up and both ends being sealed in the flame when the specimen



Fig. 161.—Raising the arm overhead, by emptying the vein, decreases the tendency to bleeding and suggillation.

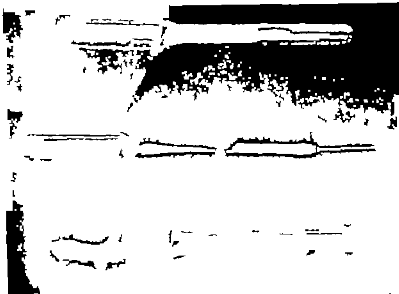


Fig. 162.—The Keidel vacuum tube for collecting blood specimens. The needle is enclosed within the sterile glass cap. The capillary neck of the glass tube, within the rubber tube, is broken or crushed *after* the tube is pinched or closed, or after the needle is introduced into the vein. The blood flows in to fill the vacuum. Clotting seals the needle and the glass cap is put on. The Corner modification inserts a glass window behind the needle to demonstrate the presence of blood (needle in the vein) before breaking the capillary tube.

is collected may be employed In newborn babies the blood may be obtained from the umbilical cord, but some investigators distrust the ordinary serological technics as applied to this blood and it is preferable to get blood later from the infant, for reasons discussed in Chapter XXI The jugular vein may be employed, and likewise the superior longitudinal sinus but these procedures are not recommended for general use

TECHNICAL ASPECTS OF FEVER THERAPY

Because of the growing field of usefulness for fever therapy in the various phases of syphilis, it is appropriate to discuss the technical aspects of this form of treatment in this chapter

The Malarial Therapy of Neurosyphilis

The status of malarial therapy from the nonspecific standpoint has been discussed in Chapter V There can be no question of the distinguished character of this contribution to the modern treatment of one of the most terrifying and hopeless phases of syphilis. It takes rank today as probably though by a somewhat narrower margin than enthusiasts admit, the most effective single method of dealing with late resistant neurosyphilis and particularly with paresis. There is, however good ground for the feeling voiced by conservative observers including Steiner in the massive Handbuch summary that a procedure such as malarial therapy which involves the inoculation of a patient with one disease to cure him of another has an intrinsically repugnant quality which, despite its effectiveness, still gives it the flavor of a makeshift. This, plus greater controllability and wider adaptability accounts for the intense interest in other forms of induced fever therapy

Historical Considerations and Earlier Literature.—The originator of malarial therapy Wagner-Jauregg of Vienna, in 1887 discussed the influence of intercurrent febrile disease upon the course of psychoses and began his experimental study by the use of Koch Old Tuberculin in the treatment of general paresis, reporting favorably on the method in 1909 Pilcz confirmed the observations of Wagner-Jauregg. Wagner-Jauregg later employed antityphoid vaccine for nonspecific effect, and finally came to the conclusion that the actual presence of an infectious disease was required for the best therapeutic results and, accordingly in 1917 took up systematically the inoculation of paretics with tertian malaria. The results in 9 instances were very favorable and continued experience of the method led him in 1921 to report on 200 cases of general paralysis, 50 per cent of which had gone into such complete remission as to be able to resume their former occupation. For his achievement Wagner-Jauregg received the Nobel prize in medicine.

The literature even up t 1936 includes almost innumerable reports of smaller groups of cases. There is definit tendency to follow the current of enthusiasm and to discuss success rather than failure, achievement rather than technic. The American experience (Cooperative Clinical Group Subcommittee on Fever Therapy 1940), comprising 1100 patients treated with malaria and 880 patients treated with artificial fever lends definite support to Simpson (1940) view that while considerable controversy has arisen regarding the relative merits of the various methods of producing artificial fever by physical means, the fact remains that the type of apparatus chosen for this work is distinctly secondary consideration. Much more important is the adequate preliminary training of the physicians and nurses ho are selected to engage in this work. In the hands of skilled orkers, employing satisfactory apparatus, few difficulties will be encountered. If however the ork is undertaken by untrained persons it is fra ght with danger

The insistent dinning of the mortality argument against malaria into the ears of its proponents is slowly leading t better evaluation of the question and clearer delineation of indications and contraindications. The argument at first advanced that the mortality of paresis itself was so high that mortality incurred in its treatment as *ipso facto* of small significance has given place to more studied consideration particularly because of the advocated extension of this well as other forms of fever therapy to the treatment of all types of syphilis. Tryparsamide ha

served as valuable foil in bringing out both the merits and the deficiencies of malarial therapy in American practice.

The Practical Equipment for Malarial Therapy.—Treatment by inoculation malaria is a specialist's method appropriate to centers and dangerous when undertaken by the inexperienced or without adequate organization and facilities. It is at its best when a group of well-organized hospitals such as some of the state groups of hospitals for the insane in this country combine on the development of a technic, draw their strain of inoculating plasmodium from a central laboratory-controlled source and the chiefs in direct contact with patients are able to give the necessary time and thought and have developed the necessary experience to meet the rather formidable array of complications which this form of treatment, especially when applied to a difficult or damaged material, will inevitably produce. While the isolated physician and the small country hospital may succeed in dealing with the earliest cases in the most robust individuals, they will inevitably be brought to book by a fatality if their success with a favorable material leads them to extend their activities into the field of the unfavorable. As many observers have emphasized and as those, such as Osborne, Cole, O'Leary, Mayne and Young and Moore in this country have clearly shown, the low mortalities of 0.5 to 1 or 2 per cent are the products of stringent selection of an appropriate material as well as experience in dealing with it.

The minimum requirements for the proper use of malarial therapy are an organized hospital service in which the chief makes daily rounds and personally sees the patients under treatment. Osborne has well emphasized this point, which Kemp and Stokes found applicable even to the relatively milder procedures of fever therapy. A successful malarial service cannot be conducted under the supervision of interns. A thoroughly trained, responsible, and autonomous nursing head is a second essential. "Breaking in" pupil nurses on sick, uncomfortable and often critically ill patients except under the most constant and expert nursing supervision, is an injustice to the method as well as the patient. A large amount of laboratory work, as will presently be seen, and the closest and most economical relationship between ward, private room, and laboratory is essential. A scale of maximum or even average charges for the repeated tests essential in the proper control of a malarial case swamps the majority of patients by its unbearable expense. Successful malarial therapy therefore has its business side, more critical sometimes even than its medical phase, and this fact alone is likely to lead to its increasing concentration in the hands of organizations and of the state. It is notable that even in a country still the center of the most individualistic type of medical practice, namely, France, steps were being taken to organize a system of centers for malarial therapy which should do away with its hedgerow exploitation by each and every individual or small group that can beg or borrow 5 cc. of malarial blood. Points at which time may be saved to the patient and, incidentally, expense, include admission to the hospital with the first chill instead of on inoculation, and the induction of febrile reaction with shortening of the incubation by the use of typhoid-paratyphoid vaccine in the malarial incubation period. Entire lack of medical supervision during the inoculation period may, however, be very serious, for apparently malarial deaths have been known to occur before the actual onset of the febrile siege.

The Field of Malarial Therapy.—General paralysis, early and late, including the field of *paresis sine paresi*, is the ideal and the chief field for malarial inoculation therapy. Subordinate to it is the group of resistant neurosyphilitic manifestations which include such conditions as primary optic atrophy and the gastric crises of tabes dorsalis. Few observers have been able to report satisfaction with their application of malaria to the treatment of tabes. Among them are Wile and Hopkins. Nonne rates malarial therapy in tabes as by no means the first choice. Bering and Dreyfus have emphasized the value of the dampened or abortive malarial course in preference to the usual siege

in patients with tabes. Not only then, is paresis the major field for malarial therapy but earlier and earlier paresis. The striking differences in mortality and therapeutic results are apparent in the tables

Malaria in Early Syphilis.—The question inevitably arises whether the use of malaria cannot be extended forward into the life history of the infection to the primary and secondary stages, both for its possible preventive value and for its aid in reversing resistant serological tests and diminishing the general severity of the disease.

This hope was extensively and enthusiastically studied by Kyrle and by Kerl. From their large experience Kerl insists that it is premature to advocate malarial therapy as protection against neurosyphilis, although its use from the second t the sixth year of the infection is rationally justifiable Several other observers have agreed that there can be no possible reason for using malarial therapy before the second year of an ordinarily progressing syphilitic infection. Von Barde found that the adenitis and eruption of secondary syphilitic infection continued to develop even when malarial therapy was used in the seronegative primary stage and instances have been observed in which malaria has induced malignant precocious tertiarism. The question as to whether previous malaria actually protects against the development of neurosyphilis must, then, be tentatively answered in the negative in spite of the often quoted statistics of Mattauschek and Pilcz, of 105 paretic army officers, not one of whom gave history of an acute febrile infection during the first few years after acquiring syphilis, while of 241 syphilitic patients ho had cute infectious diseases during that period, not one developed general paresis. Kirschbaum, in contravention of this conception, reports 10 patients with general paresis who had had malaria during the secondary stage of their syphilis W have moreover seen confirmation of the belief that patients who have had malaria in early lif derive little benefit from it and i some cases are markedly resistant even to infection with it (Greek patients particularly among whom malaria was prevalent) when they later develop paretic neurosyphilis.

It is then, we think, safe to say in accordance with Zieler s summary of the literature that there is no justification for the routinization of malarial therapy no reason for its extension to the treatment of early syphilis especially as a substitute for thoroughgoing treatment with arsphenamine, bismuth and mercury and that its primary and established field of usefulness is paresis and preparesis, other aspects of established neurosyphilis in relation to its effectiveness being still under study and not fully evaluated. The combined treatment of early syphilis with other types of fever and chemotherapy may prove to be one of the most efficient modes of dealing with the disease as a whole.

Indications and Contraindications.—These we have attempted to summarize in Fig 153 certain points will bear special discussion The control of the strain of malarial organism will be presently mentioned, but it should be understood more generally that unless a reliable strain of fairly constant characteristics is being maintained or can be procured from a center dangerous and disconcerting results may ensue. Wagner-Jauregg especially emphasizes that no person who has ever been in or near the tropics should be allowed to serve as a donor no matter what his condition, and mosquito inoculation should be condemned on the score of the presence of sexual forms which conduces to relapse of the inoculated malaria after treatment with quinine. Wagner-Jauregg has also emphasized the importance of blood-grouping in advanced inoculation and the use of a donor of a different group from that of the patient in order to prevent the appearance of a quotidian type of fever with its exhausting daily attacks. Moore (text, 1941) on the other hand notes increased facility of inoculation and shortened incubation when the donor is of the same blood group using a large inoculum.

The question of an age limit for malarial therapy is a difficult one. The known extensive character of cardiovascular involvement, probably the gravest single contraindication to any form of fever therapy in patients with long standing syphilitic infections, and the very great difficulty of accurately evalu-

Fig. 185.

MALARIAL THERAPY

Indications	Contraindications
1. Early paresis and preparesis in young robust persons.	1. Decentralized inexpert control and inadequate facilities (not practitioner's method).
2. The same conditions in older patients without contraindications.	2. Unsatisfactory strain of malarial organism.
3. Presence of neurosyphilitic or other optic nerve disease contraindicating tryparsamide.	3. Donor of same blood group as patient (Wagner-Jauregg).
4. Resistant nonparetic asymptomatic neurosyphilis (in late latency, not early syphilis).	4. Old age. The age limit should be based on physical status rather than years.
5. Where a reasonable trial of tryparsamide has failed (one year) and no serious contraindications to malaria appear.	5. Definite cardiovascular disease, especially coronary and myocardial, and including arteriosclerosis.
6. Optic atrophy and gastric crises, persistent lightning pains when not otherwise contraindicated.	6. Pulmonary tuberculosis, latent or active.
	7. Chronic alcoholism.
	8. Marked diabetes (mild is not).
	9. Severe anemia.
	10. Obesity.
	11. Persistent thymus.
	12. "Galloping" paresis.
	13. Advanced tabes with severe ataxia, decubitus, pyelonephritis.
	14. Pregnancy.
	15. Kidney disease.
	16. Marked hepatic disease or insufficiency or splenic disease.
	17. Severe debility.
	18. Last stages.

Discussion

1. Advantages of malarial therapy. On the whole, probably the highest effectiveness, risks disregarded, of any single form of treatment for resistant neurosyphilis; accomplishes much in a short time; institutional features control therapeutic flare-up without family and social difficulties, places responsibility and control in hands of experts; the best single chance for result in difficulty controllable or uncooperative cases.
2. Disadvantages of malarial therapy. A center or institutional method, for the experienced only; not always available; mortality 0.5 to 10 plus per cent; temporary dislocation of occupation and economic status, some stigmatization; difficulty of maintaining safe strains of organism in small institutions; discomforts of stormy course; not adapted to the debilitated, badly complicated case.

ating such involvement has led us, from a limited number of personal observations, to set age forty-five as an approximate limit beyond which anything approaching the over-ready or routinized employment of malaria becomes particularly dangerous. None the less it is true that patients as old

as seventy years have undergone malarial therapy without ill effects but such occasional strokes of luck are by no means guides to an intelligent therapeutic procedure Perhaps it might fairly be said that the age limit should be based upon the physical characteristics of the patient rather than his years, for the obvious differences in the resistance and physical resources of two different types of the same age is too evident to need comment.

Cardiovascular disease, and particularly coronary and myocardial insufficiency is the greatest single outstanding contraindication to malarial therapy Generalized arteriosclerosis is perhaps of equal seriousness. The cardiovascular involvement need by no means necessarily be syphilitic—in fact we have seen that certain observers rate cardiovascular syphilis in conjunction with neurosyphilis as of a relatively less advanced and serious type Steiner however states that by far the largest proportion of the deaths in the literature have a cardiovascular slant, and emphasizes the difficulty of using any criteria dependent on sharp differentiation between uncomplicated aortitis and aortitis with coronary involvement and myocarditis Wagner-Jauregg, in his more recent statements believes that vascular syphilis in patients with paresis is often made worse rather than better by malaria. Moore s very instructive case (Moore Danglade, and Reisinger) in which a patient with grave cardiovascular syphilis was wheedled through two malarial sieges, is, however an excellent illustration of the possibilities under expert care, and with the use of quinine or bismuth to diminish the severity of the chills and control their frequency it may be possible to carry a patient through two short malarial sieges instead of one longer one. In fact, Wagner-Jauregg recommends this method for more general use in preference to the severe strain upon the patient s organization of a continuous session of 16 to 18 chills. Kihn believes that the really serious cardiovascular risks to the patient come at the close of the malarial siege as quinine is being used, and advocates initial small followed by later heavier doses as a method of "sliding the patient out" of his malaria.

Pulmonary complications rank high among the serious incidents of malarial therapy and even the milder forms of fever therapy have, in our experience, *shown a definite tendency to light up latent tuberculous foci at the apices* The presence of active tuberculosis is therefore generally accepted as a strong contraindication to malarial therapy and the more conservative general reviews include known latent tuberculosis also

There is a definite rise in blood sugar during fever therapy and mild diabetics can have this complication controlled by insulin. In the graver cases, with their presumed arteriosclerotic damage and susceptibility to intercurrent infections, malarial therapy is definitely contraindicated.

Moderate grades of anemia do not contraindicate malarial therapy provided an adequate microscopical control of the blood is exercised. Schilling observed the marked tendency toward regeneration in the anemias of induced malaria, so that the complication need rarely be serious.

The remaining list of contraindications includes the major items about which differences of opinion exist. Kirby rates the mild jaundice frequently seen in malarial patients as of small importance, while Osborne, on the other hand, stresses the importance of watching the liver and spleen, which enlarge in from 5 to 10 per cent of patients and of taking frequent icterus indices and van den Bergh tests. Wile and Mundt (1941) report rupture of the spleen. The importance of kidney failure is emphasized by the attention which is paid

to frequent blood urea estimations. Rapidly progressive neurosyphilis and in particular so-called galloping paresis is usually made rapidly worse by malaria as, indeed by most other forms of treatment. While the early tabetic may respond favorably the advanced case is subjected to grave risks quite out of proportion to the probability of improvement.

The Technic of Malarial Therapy

The Organism—Type Source Choice Preservation, and So Forth.—*Plasmodium vivax* the organism responsible for tertian malaria, is the one usually employed in the malarial treatment of neurosyphilis. Quartan malaria (*Plasmodium malariae*) may be used in Negro patients in certain patients immune to tertian infection or in cases where a milder malarial disease is desirable (certain debilitated persons) (Boyd 1934 Branche 1934 Young *et al.* 1940 Fong 1940 Kroll 1940 and others) Ape malaria (*P knowlesi*) has not been widely used (Ciuca *et al* 1937 Milam and Kusch, 1938)

When mosquito-borne organisms are used, the sexual phase of the life cycle is introduced into the situation, whereas if the infection is transmitted by an old strain that has passed exclusively from man to man by inoculation, there is a tendency for the sexual phase to die out, leaving a pure asexual strain which produces a milder and more uniform course and less tendency to relapse after quinine.

Opinions differ somewhat on this point. Rudolf, for example, reports on strains carried in the British hospitals for as long as three and four years with the continued appearance of sexual forms after more than seventy passages. Kopeloff, Blackman, and McGinn have reported on two American strains which became completely asexual after two and one-half years of continuous use in the hospitals of New York State.

It thus appears that the use of a well-established and biologically adapted strain of organism such as can usually only be obtained through continuously functioning institutional sources, is an important asset in the malarial therapy of neurosyphilis and an additional reason for its institutional control. It would seem almost unnecessary to issue the warning that haphazard inoculation from individuals whose strain of organism has not at least been examined as a preliminary or who have been in the tropics and may be the bearers of the malignant estivo-autumnal type should not be practiced. In all cases where a strain is being carried, a properly equipped laboratory should periodically check the characteristics of the organism.

Mosquito transmission is in general, therefore, not desirable though there has been some hope that it might contribute to the problem of maintaining a reservoir for infection where relatively few malarial treatments are given on a service This question is discussed by Rudolf, Gerstmann, Steiner and others.

An important aspect of mosquito transmission concerns the fear which has existed that the establishment of centers for malarial treatment would be in effect that of establishing centers for the dissemination of malaria to the surrounding population. Screening of patients should be practiced during the summer months and the British Board of Control, for example some of whose centers are in regions in which Anopheles is prevalent, insists on strict observance of this rule. A weekly search of the patients rooms is made and patients in well-lighted rooms are allowed to be around without net protection during the daytime inasmuch as the insects bite only at night. While in temperate climate there is less concern about accidental transmission of malaria, Mayne and Young, working in South Carolina, insist vigorously that wards and rooms must be screened, and cite European epidemics resulting from carelessness in this regard.

Malarial blood for inoculation purposes may be transferred from one patient to another by the addition of an equal quantity of 0.5 per cent sodium citrate solution or following defibrination by a glass rod (five minutes stirring) If kept against the person of the messenger to keep it warm it may be sent for considerable distances. Frozen, defibrinated blood has been sent by mail over considerable distances Mayne and Young describe two methods as follows (1) The vials of blood are packed in rubber finger-cots wrapped in gauze and then packed securely in crushed ice in a wide-mouthed vacuum

bottle The bottle is then placed in a specially made shock absorbing card board container The main objection to this method has been the breakage of some containers despite all possible care in packing (2) A less expensive method and one that appears to be quite satisfactory makes use of the Army Medical School water shipping containers These consist of an inside water tight metal screw-top tube 2 inches in diameter and 8 inches long and an outside cardboard screw top mailing tube. The vials are wrapped as above and packed tightly in crushed ice in the inside metal container Successful shipments have been made to great distances in this country These authors defibrinate the blood by shaking with glass beads or anticoagulants (2.5 per cent sodium citrate, 70 cc. to 500 cc. of blood) This may be put up in 5 cc. vials for use or shipment. Stored at 40° F the plasmodium is viable up to 14 days. At room temperature, virulence is retained for from twelve to twenty four hours, but decreases considerably in the longer period. With defibrination and refrigeration in Ringer's solution diluted with donor's inactivated serum sixty to sixty-two hours is the limit (Gerstmann) A virulence retained for forty-eight to seventy four hours is possible with Gerstmann's blood agar method (Rudolf) Kauders's method mixes the blood with Merck's pure gelatin (2 cc. in 10 cc.) with solidification Before use it is melted at 28° C

Inoculation Methods.—Subcutaneous inoculation is preferred by most recent authorities. Intramuscular inoculation is the equivalent of subcutaneous inoculation. Wagner-Jauregg gives subcutaneous preference over intravenous inoculation which he believes leads to quotidian or daily chills. Gerstmann recommends 1 to 4 cc., and Graff 3 to 5 cc Wagner-Jauregg believes that larger inoculations also tend to bring on the quotidian type of reaction. The site of inoculation is unimportant, but Gerstmann, in addition to subcutaneous injections, rubs in a few drops on a scarified area of the arm Intravenous in oculation as used by Gerstmann in doses of 0.5 to 2 cc., and Driver Gammel, and Karnosh have used up to 8 cc. The shortened incubation period is not necessarily an advantage even in rapidly progressive cases. Intracutaneous inoculation, while lengthening the incubation period gives a higher proportion of tertian fever Intraspinal inoculation leads to a high proportion of grave complications (Benedek-Steiner)

Incubation.—For subcutaneous inoculation Rudolf gives 38 to 46 per cent, showing the first clear-cut temperature rise within ten days 41 to 46 per cent in eleven to twenty days and 8 to 10 per cent in from twenty-one to thirty days. The first rise in temperature is not necessarily malarial Plasmodia tend to appear in the blood about the time of the first actual malarial attack. The incubation period for intravenously inoculated quartan malaria (U S. Marine Hospital strain, Charleston, S. C strain) is an average of 15 4 days (ranging from 8 to 28 days) for white patients, and 19.5 days (2 to 65 days) for colored patients (Kroll, 1940)

Malarial Immunity Abortive Cases, and Reactivation.—Immunity t insect-borne and inoculation malaria undoubtedly exists, but is uncommon. Plasmodia may be present in considerable numbers in the blood and the patient may show the clinical improvement characteristic of malarial stage without having been through the normal course of chills and fever Brustch, for example, reports such case with physical and mental improvement and serological return to normal. As rule, immunity t malaria, even in malarious populations, is comparatively slight, but inoculation failures as high as 5 in number have been reported Gerstmann believes second inoculation attacks to be milder than the first (Rudolf, p 67) There is tendency to spontaneous cessation of the fever in second attacks When the same strain is used in second inoculation, parasites may appear in the blood but the percentage incidence of pyrexia with various authors

varies from 0 to 100 per cent. The virulence of a strain of inoculation malaria does not appear to change materially and is certainly not increased by repeated passage through man. The Vienna strain has undergone little or no alteration, Yorke and MacFie found no alteration in forty passages during three years. O'Leary has observed no accentuation, and some strains have even been reported as becoming attenuated.

Failure of Inoculation.—Failure of inoculation is not always due t immunity If the donor has been receiving antimalarial treatment either with quinine or the arsphenamines, the inoculation is apt to fail, and the same is true of the recipient. Bismuth should also be thought of A hot syringe or antiseptic on the glassware or apparatus will cause failure. Rudolf believes that hemolysis of the blood is an unfavorable circumstance. In reinoculations new strain of parasite should be used.

Activation.—I unsatisfactory cases an effort may be made to activate the malaria by injections of sodium nucleinat after the method of Schlesinger and Kogerer or of milk intramuscularly (2 to 10 cc.) or of typhoid vaccine, method not free from danger inasmuch as we have seen fatal collapse without rise of temperature occur following typhoid vaccine in the incubation stage of quartan malaria. This method may also be used to give the patient the benefit of nonspecific proteins during the incubation period but is seldom practiced.

Onset and F brile Reaction.—The phenomena attendant on the incubation and course of malarial pyrexia have been closely studied by Rudolf. Prepyrexial rises of temperature during the inoculation period may occur in paretics, or the temperature may be normal or subnormal *It should be taken every four hours throughout the entire course from inoculation to the termination of quinine* Occasional slight improvement in the mental condition of the patient may appear in the incubation period. Before the onset of the typical attack the patient feels out of sorts with headache and neuralgic pains, and when the rigor develops usually looks profoundly ill, the lips and nails cyanosed and the extremities cold. The violence of the chill is sometimes astonishing and the duration varies from few minutes to two hours or more, veraging less than an hour While the patient is still shivering, the temperature begins to rise the patient is more comfortable, but presently the skin becomes dry the face flushed, and the head throbs. Marked thirst develops and the temperature reaches its maximum followed by sudden decline in tertian cases (persistent high fever in estivo-autumnal contaminations) and profuse sweating occurs Marked variations in individual cases occur The temperature does not usually reach its maximum with the first attack and there may be one or more milder and somewhat irregular rises before the fever settles out the typical tertian swing Large rises on one may be succeeded by small rises on the next, or a typical quotidian form may be carried throughout Wagner-Jauregg believes this daily rise t be too exhausting and that such cases should be terminated after short course when their character is clearly defined The use of bismuth preparations, especially thiobismol, to temporarily suppress the malarial chills has been previously mentioned (Cole, *et al* Schwartz.) I typical benign tertian fever the pyrexia is short, the temperature during the interval sometimes subnormal, and the succeeding chill may occasionally be delayed by twenty-four hours

Temperature should be taken every thirty minutes to an hour during the febrile stage.

Management and Complications.—The recognized complications of malarial therapy are enumerated in Fig 154 The inoculation problems have been considered If the patient is robust, the quotidian type of fever may be well borne, but if it is not, a single dose of 3 to 4 grains (0.2–0.3 Gm) of quinine as recommended by Wagner-Jauregg or of bismuth thioglycollate (0.2 Gm of the salt intramuscularly one dose only) will give a brief remission of two or three days after which a milder form is likely to reestablish itself Quotidian attacks can be avoided by subcutaneous injection of small doses and a donor of a different blood group (Wagner-Jauregg) The beginning of the adequate pyrexial range is at 101 F and a temperature of 106° F is the maximum for safety at which point cold sponges or a pack should be employed to bring down the temperature. When the rectal temperature falls to 102° F., the antipyrexial measures may be discontinued but the effect is usually only temporary and the hydrotherapy must be repeated Rudolf gives a serviceable rule for safety limits—"the three sixes, 106° F., 100 and 60 " representing temperature, pulse and respiration respectively

Blood pressure should be taken with the temperature during the attack, and daily between paroxysms. If it falls below 80 mm. systolic the siege should be terminated. O'Leary and Driver Gammel and Kerneck and Paige Bickloff and Osborne believe that the siege should be immediately stopped if the blood urea rises above 75 mg. per cent. This may occur without recognizable abnormality in the urine.

Blood and urine should be examined three times weekly and a rapidly progressing anemia calls for cessation of the paroxysms. Albuminuria usually develops toward the end of the siege

Fig. 134

COMPLICATIONS IN MALARIAL THERAPY

1. Neurological and Psychic.
   Delirium, hallucinosis, excitement, exaggerated or appearing for the first time with onset of fever or during the period of incubation. Depression and attempted suicide. Safeguard the patient. Focal symptoms from nervous system, paralysis, convulsions, apoplectiform seizures, crises, lancinating pains.
2. Cardiovascular.
   Myocardial collapse
   Falling blood pressure below 75 mm. systolic the danger point.
      Daily observation.
   Transient benign edema.
   Tachycardia, 160 upper limit of safety
3. Pulmonary
   Bronchitis, bronchopneumonia, lobar pneumonia.
   Lighting up of latent or active tuberculosis.
   Edema secondary to cardiac failure
4. Nephritic.
   Rising blood urea (75 mg. per cent upper limit of safety)
   Nephritis.
   Cystitis, ascending urinary tract infection.
5. Liver and spleen.
   Hepatic injury enlargement, rising icterus index (take twice weekly), jaundice
   Splenic enlargement and (rarely) rupture
6. Gastro-intestinal.
   Uncontrollable diarrhea.
   Melena.
7. Hematogenous.
   Progressive severe anemia. Blood count three times weekly
   Fall below 2,000,000 red blood cells dangerous.
8. Malaria per se.
   Inoculation with estivo-autumnal strain of Plasmodium.
   Daily chills instead of alternate days (tertian vs. quotidian type).
   Hyperpyrexia.
   Quinine idiosyncrasy
   Recurrence of malarial infection (usually in mosquito-infected patients—Davidson)
   Prostration terminating in coma (loss of strength between paroxysms of fever first warning
9. Herpes.
10. General.
   Lighting up of other infections, particularly focal.

and glycosuria may be present but is usually without significance. American observers emphasize hepatic injury though Kirby states that the mild jaundice that complicates a number of cases is without significance. Paige, Bickloff and Osborne found marked enlargement of the liver and spleen in 5 to 10 per cent of cases. The icterus index should be taken once or twice a week and readings above 40 call for termination. Red blood cell counts below 2,000,000 require quinine (see p. 343). Rudolf, however rates skin jaundice as a serious sign (conjunctival less significant), though Gerstmann minimizes it. Jaundice without parasites in the blood stream and without fever has occurred and has cleared up under quinine. Splenic enlargement may lead to rupture

i restless or overactive patients, ho should be kept specially quiet. Smear examinations of the blood for parasites re considered by some observers as daily necessity and marked sudden increase in number of parasites as warning for terminating the siege

Pulmonary Complications.—This constitutes an important group rated by Hinde and Blalock as responsible for 11 per cent of deaths after fever therapy The complications may be of three types Edema or pulmonary congestion secondary to cardiac insufficiency; bronchitis, bronchopneumonia, or lobar pneumonia, and focal lighting-up of pulmonary infections already present, including tuberculosis. Rudolf considers pulmonary embarrassment in the ordinary course of treatment, represented by respiratory rat of 60, as an indication for immediate termination of the siege. A wet lung should be interpreted in terms of the heart. Definit localizing signs call for termination of the attack, usually however too lat to void the complication. On tw occasions w have seen apical tuberculosis flared up by fever therapy in one of them the condition previously unrecognized. While the milder courses of treatment given at Vienna have led Gerstmann and others t disregard pulmonary tuberculosis as a complication and, in fact, have enabled them t show instances of satisfactory therapeutic results in such cases, even with improvement of the t berculosis, such latitude is not advisable in general or particularly in America practice ith its tendency to longer pyrexial sieges.

Other Focal Infections.—Arthritis may flare up under malarial therapy and under forms of fever therapy but this is not necessary contraindication. I cases of tabes, however the presence of pyelitis and pyelonephritis is grave contraindication to malarial therapy and Moore has *observed t deaths in a small series from this cause.*

Renal Complications.—These are uncommon though the majority of malarial patients show some albumin nd casts toward the end of the pyrexial siege. Chronic nephritics, however, are t be regarded as ineligible for malarial therapy both because of the kidneys and the heart status of such patients.

Complications in the Nervous System.—These constit te i all probability the largest and most important group. Seizures of various types are quite common in malarial therapy nd are not necessarily t be attributed to the treatment. Steiner Kirby and Rudolf regard them as serious. Steiner believes, however that they may have therapeutic shock significance. Rudolf points out that they may be followed promptly by secondary bronchopneumonia. The poplectiform seizures may leave residual paralyses or may follow the relatively benign course of the paretic epileptiform ttacks.

Excited paretic patients very frequently go int delirium with hallucinosis, extreme excitement and mania hich requires restraint but may subside bet een paroxysms and in any case usually disappears promptly toward the close of the malarial siege or shortly thereaft I fact, it is the initially excited cases hich have the best all-around prognosi Depression with suicidal tendencies may be serious and must be closely watched.

Collapse and Myocardial Failure.—This grave group of complication may present either sudden rapidly progressive drop in strength, as emphasized by Rudolf the symptom continuing bet een the pyrexial attacks rather than during the ttacks; or it may take the form of typical myocardial collapse with rising pulse rat edema, accumulation of fl id in the lungs, and enlargement of the heart or it may present the collapse picture with pallor grayness and cyanosis, and the Hippocratic facies. The anticipated strain on the cardiovascular mechanism is evidenced by the frequent practice of digitalizing patients or giving strophanthus more or less routinely during the incubation period If signs of cardiac eakness ppear the siege should be stopped t once Obese patients are placed in the contraindicated group by most observers, because of their fatty hearts

Kirby rates the transient edema observed in some patients, however unimportant

Arteriosclerotics are of course, subject to apoplectiform attacks and are placed in the contraindicated group

Gastro-intestinal Reactions.—Obstinate vomiting may occur but is unusual in benign tertian malaria, though not uncommon in the estivo-autumnal type. There have, however been number of reports of severe diarrhea (Kihn) and intestinal hemorrhage, grave complication hich may terminate fatally

Quinine Idiosyncrasy—This important though not common complication should really be detected before treatment is begun by the administration of small test dose of quinine. The recognized symptoms of the idiosyncrasy include severe nausea, vomiting or diarrhea; skin eruption, usually scarlatiniform or urticarial, ringing in the ears, dizziness and deafness; impairment of vision dyspnea asthma, and hemorrhages Stitt describes the skin test for idiosyncrasy employing 1 t 10 neutral solution of quinine rubbed int scarified area on the forearm, with a control of normal serum Rudolf reports the successful use of Stitt desensitization procedure hich consists of giving ½ grain (6 mg.) quinine ith 5 grains (0 3 Gm.) sodium bicarbonate

followed an hour and a half later by 1 gram of quinine with an equal amount of sodium bicarbonate.

Recurrence of the Malarial Infection.—This is rarely observed in the benign inoculation types employing blood transmitted from patient to patient.

Management of the Average Patient During the Siege.—The patient should be kept in bed during the febrile period. The temperature should be taken hourly. The blood chlorides should be maintained by a daily ingestion of 6 Gm., with abundant fluid, to replace the loss by sweating. Wile and Mundt (1941) emphasize the danger of chill with low temperature and unusually high pulse and respiratory rate and fever which remains for eight hours after the normal chill peak. Mild icterus is less important, but severe icterus with index above 50, red cell count below 2,000,000, progressive rapid anemia with cessation of chills and profuse diarrhea with vomiting and dehydration constitute serious signs. For peripheral circulatory collapse, transfusion is advocated and Pracy (1943) reports the value of blood plasma in combatting shock which though advocated for physically induced fever should be applicable to malaria. Gerstmann recommends tincture of strophanthus, 10 minims, at the height of each attack, and digitalis, powdered, 1½ grains, may be given twice daily as a preparation in patients in whom cardiac indications exist. Amidopyrine gives relief for the headache if not contraindicated, and sodium bicarbonate may be used for the nausea. Rudolf recommends sugar solution by mouth every two and one half hours, and states that patients feel sustained by it. As sedatives in marked excitement, morphine and hyoscine may be used, and the more powerful cyclobarbital derivatives may be used for the delirium. The dose must be considerably larger than the average. Fluids are forced, the diet should be light during the paroxysms, and cold packs or the administration of a single 2-grain dose of quinine controls the hyperpyrexia and the frequency of the attacks, in stormy cases.

Optimum Fever Levels.—According to the Subcommittee on Fever Therapy of the Cooperative Clinical Group (1940) the highest percentage of clinical remissions was obtained in patients treated with an average of sixty-nine hours of fever above 101° F (38.3° C.), of which total fever time 70 per cent was at a level above 105° F (40.6° C.) with a maximum temperature of 106.9° F (41.6° C.). Equally good results were obtained in patients treated with an average of forty-four hours of fever above 101° F (38.3° C.), of which total time 57 per cent was above 106° F (41.0° C.) with a maximum temperature 107° F (41.7° C.). They were of the opinion that fever administered at levels above 106.7° F (41.5° C.) introduces unnecessary hazards. On the other hand, Kopp and Solomon (1939) found from their 163 paretic patients to whom malaria was given, the amount of fever received at temperature levels of 104°, 105°, 106° F and above did not make any significant statistical difference in the clinical results obtained. The best clinical results were obtained when more than 150 hours over 100° F were experienced.

Length and Termination of the Siege.—American and European practice seem to differ on this point. Wagner-Jauregg's most recent writings advocate two mild siegs of malaria in preference to one intense one, and Viennese practice has rarely exceeded eight or ten fever paroxysms in any one session. On the other hand, American malarial therapists employ twelve to eighteen paroxysms. The general condition of the patient and the end to be attained must be considered in each case.

The termination of the malarial siege is accomplished as a rule by the administration of quinine. A number of dosage systems are in existence. Caccial, quoted by Rudolf, found that the smallest number of relapses (15 per cent) occurred in cases who were given 23 to 30 grains of quinine every day for from seven to ten days. The dose required varies somewhat with the strain. It is rarely necessary to give the drug otherwise than by mouth; the sulphate or bisulphate is satisfactorily dispensed in capsule or in solution in a large amount of fluid. Some observers recommend a preliminary cathartic. Typical dosage scales are the following: 10 grains (0.6 Gm.) of the bisulphate twice a day for three days, followed by the same dose once a day for fourteen days, a total of 200 grains (12 Gm.) (Rudolf). Five Gm. of the sulphate in seven days, using 0.5 Gm. twice a day for the first three days (Steiner). 10 grains three times a day; 10 grains quinine in seventeen days, using 0.5 Gm. twice a day the first three days, and 0.5 Gm. once a day the remaining fourteen days (Gerstmann). Mahlens and Kirschbaum employ a broken-dosage system of 1 Gm. in seven to three days with six or seven quinine-free days between, to a total of 15 or 16 Gm. The dihydrochloride, 0.5 Gm. once or twice daily intravenously may be used under special circumstances.

Antimalarial Substitutes for Quinine.—Various synthetic substitutes for quinine have been proposed. Atabrine di-hydrochloride (dose 0.1 Gm. 3 times daily after meals for five days) is the most acceptable so far. Totaquine and plasmochin may be used but the latter with atabrine, never.

The present emergency has curtailed the use of quinine or even atabrine di-hydrochloride with the result that drugs having some antimalarial action are being examined. Bismuth thio-

glycollate has been suggested. Neoarsphenamine was evaluated from the antimalarial standpoint years ago and found ineffective. Goldman (1938) and Young and McLendon (1939) have tested mapharsen from this standpoint, the former with enthusiastic approval, the latter without success. The latter authors took pains to control their use of arsenoxide and tryparsamide for the termination of quartan malaria; reexamination of blood smears as long as twenty-two weeks after the completion of the mapharsen course showed all of their patients to be asymptomatic malarial carriers. The failure of tryparsamide as an antimalarial agent was demonstrated in the same way. The sulfonamides have been shown to have mild antimalarial action (Coggeshall *et al.*, 1941, Rogers, 1941) but Gibbs (1940) rates them as ineffective. In general it is wiser to employ other method of fever therapy than malaria during the extreme scarcity of quinine.

Postmalarial Treatment and Treatment Combinations.—As O'Leary well points out, induced malaria is not an exclusive form of treatment. Viennese practice has followed the malarial course by neoarsphenamine, 0.3, 0.45, and 4 injections of 0.6 Gm. at weekly intervals (Wagner-Jauregg). There were, however, early differences of opinion in regard to postmalarial arsenical therapy. Gerstmann and Nonne believed that it was unimportant. Dattner (quoted by Rudolf) found 25 per cent of general paralytics treated with malaria alone return to their previous occupations, *whereas 40 per cent of those treated with malaria and arsphenamine did so.* The London County Mental Hospitals' figures gave 33.6 for the first group and 41.7 for the second. O'Leary and Goeckerman who at first opposed, now advocate, postmalarial arsphenamine therapy. Osborne advises at least two or three courses of arsphenamine and bismuth. Kanders takes a similar position.

Particular interest attaches, of course, to the increasing practice of employing tryparsamide following malarial therapy. On this practice a favorable opinion is definitely crystallizing, reinforced, especially, by such painstaking studies as those of Hinds and Blalock and Poole. Methods and results are discussed under Combination Therapy.

Constitutional Gains Following Malarial Therapy.—These are often striking and, according to Wagner-Jauregg, more likely to follow the shorter and milder courses, which he recommends (8 to 10 chills). So striking is the gain in weight and well-being in some patients that it has been spoken of as "resurrection." This gain in physical well-being may take place even without any corresponding mental improvement.

General Principles of Postmalarial Therapy.—The general principles applicable to this question of postmalarial therapy are essentially these. The earlier in the course of a syphilitic infection or the more clearly other evidences of syphilitic involvement besides the cerebral phase present themselves, the more essential is painstaking and intelligent postmalarial treatment with the arsenicals, mercury and bismuth. The patient's syphilitic infection should be treated as a whole; the individual indications should be followed, as in the use of intraspinal therapy, for specific symptoms of low tabes or for primary optic atrophy concurrently present with the paresis; and the ability of malaria to induce allergic relapse, to stir up without silencing both cutaneous and visceral processes, and to injure the cardiovascular system (Wagner-Jauregg) must be borne in mind as a proper justification for general antisyphilitic treatment following inoculation malaria. The amount and kind of the treatment applied will depend upon the indications in the particular case and should, generally speaking, include not only arsphenamine but heavy metal therapy.

The repetition of the malarial siege may be attempted where the results of the first session were unsatisfactory and the condition of the patient warrants. Inasmuch as a tendency toward, though not an absolute degree of immunity is established by the first infection, it is desirable, if possible, to use a different strain of *Plasmodium vivax* for the second inoculation or resort to quartan malaria. A single failure to reinoculate should not necessarily discourage a third, fourth, or even fifth attempt, but the necessity for reinoculation is diminishing with the improvement of non-specific methods for in-

ducing fever and the collateral use of tryparsamide. The outlook for successful reinoculation increases with lapse of time since the first siege.

Mortality of Malarial Therapy—In dealing with a condition such as general paralysis, which has a high mortality of its own, it is extremely difficult to interpret the mortality situation for any form of treatment as such. None the less, we have made the attempt for the mortality issue is after all, one of the most critical in the estimation of malaria as a therapeutic procedure. In Fig 155 which represents in general the routine initiated application of

Fig 155

RESULTS IN MALARIAL THERAPY

Reported by	Total number cases.	Complete remission per cent.	Partial remission per cent.	Worse or stationary per cent.	Deaths' per cent.
Jahnel (after Kraepelin)	3138	27.5	20.7		
	1683	37.0			
Gerstmann	400	33	14	43	10
Gerstmann.	31	83.8	10.83		
	Early				
Pulocker	441	11	31	11	38 Direct
O'Leary and Brunsting	100	38	31	17	14
O'Leary	88 Asymptomatic	34	14	52	0
Kirschbaum	196	31	32	23	15
Kaldewey	94	33	10	46	10.5 Direct
Kirby	141	38	21	25	19 9 Direct
Herrmann	43 Advanced	4	31	23	40
Herrmann	10 Early	90	0	0	10
Green	80	26	34	26	14
Wile and Davenport	45	67	13	13	7
Average		39.1	31.6	28.1	12.7

Deaths occurring during the malarial treatment or as a direct result of it are marked direct. Further figures concerning the mortality of malaria *per se* are those of O'Leary 1 per cent; Cole, 0.5 per cent; Osborne, 2 per cent. Osborne quotes O'Leary as stating that he has not had a malarial death in his last 200 cases. The studies of Gerstmann from Wagner-Jauregg clinic and of O'Leary are especially valuable in that their figures are based on cases followed from at least two to as long as seven and one-half years after malarial treatment.

Percentages do not total exactly 100 because of decimal losses in refiguring to the table headings from the publications. In some cases the discrepancies are the authors.

malaria to the treatment of general paresis, the wide range must be apparent, and an average can be no more than the merest approximation. It is interesting that the Cooperative Clinical Group's Subcommittee on Fever Therapy (1940) found the crude death rate from malaria to be 13 per cent. Deaths occurring between inoculation and the onset of the fever should not be regarded as malarial, at least if no plasmodia are present in the blood. Deaths during the malarial siege are generally accepted as due to the treatment. The crux comes in the postmalarial deaths, in which the reduced resistance of the patient to intercurrent infections begins to take its toll. In fairness it seems to us that

many of these deaths must be attributed to the form of treatment, though there is a distinct disposition on the part of some authors to minimize or disregard them Rudolf's excellent analysis of deaths before and after onset shows the importance of pneumonia, cerebral accidents, progressive weakness and cardiac failure before the first febrile attack, and the same element after the siege The argument that the mortality of paresis is enormous at best, and *that therefore the smaller comparative malarial mortality is of no significance*, impresses us as specious when there exists, as in this case, a choice of a method like tryparsamide with lower mortality less tax on the resistance of the individual, and *in many cases outright constitutional tonic effects.* Wile and Mundt (1942) found a mortality rate of 2.8 per cent (29 of 1026 patients) Although only 35 per cent of their patients had paresis, 60 per cent of the fatalities occurred among them. The figures of Kryle (0.98 per cent) and the more recent statements of Osborne, Cole, Driver *et al.* and O'Leary and associates (CCG 1940) and Wile and Mundt (1942) are representative of malarial therapy under the best conditions of selection and in early often asymptomatic cases, so that they are not properly comparable with those obtained in institutions for the insane. They are, however the figures toward which we should strive by the increasingly early application of malarial therapy on proper indications, in the course of the individual case

OTHER INFECTION PRODUCING METHODS OF TREATMENT IN NEUROSYPHILIS

The improvement of psychoses through intercurrent febrile infections is a matter of long standing observation, far antedating the introduction of inoculation therapy and, in fact, it was these scattered observations which led Wagner-Jauregg to put malarial therapy finally to the test. One of us (JHS) has observed striking improvement in a paretic patient following an extensive erysipelas covering the entire back. In another patient, now well and active, a severe pyelonephritis with high fever lasting for several weeks, initiated an improvement which was consolidated by the use of tryparsamide Recurrent fever induced by strains of the African spirochete, *Spirochaeta duttoni*, has achieved some popularity in Europe following the introductory work of Plaut and Steiner This organism can be carried in the laboratory in mice for inoculation purposes and produces typical relapsing fever in which the intervals between the pyrexial sieges are longer than in malarial therapy If mouse blood is used for inoculation, care must be taken that no other pathogenic organisms are present. The incubation period averages four to five days, the infection may persist long after the final febrile seizure, and the cerebrospinal fluid is invaded in the course of the disease. Recurrent fever has a number of disadvantages, including its erratic and prolonged course, the fact that there is no means of terminating it short of the spontaneous recovery arsphenamine being ineffective for the purpose. Reinoculation is also impossible, but natural immunity is rare. The complications in general are somewhat less severe than those of malaria, and the therapeutic results, to judge by Steiner most recent summary less good than those of malaria, in the majority of cases. The method, therefore as matters stand today does not seem likely to achieve any wide popularity

As an alternate to malarial therapy Solomon, Berk, Theiler and Clay investigated sodoku, which is the Japanese name for rat-bite fever *Spirochaeta morsus-muris* can be carried as a laboratory strain in guinea-pigs, but the fever produced by it in man, while very satisfactory in some cases, is erratic and inadequate in others, and the method is at best a poor second to malaria, unlikely to achieve widespread adoption The fever is readily terminated with arsphenamine and the constitutional symptoms are as a rule very mild

NONSPECIFIC PROTEIN IN THE FEVER THERAPY OF NEUROSYPHILIS

Typhoid Vaccine —The induction of fever by the use of typhoid or mixed typhoid-paratyphoid vaccine was among the earlier ones studied by Wagner Jauregg It presents certain definite advantages, including the fact that no *strain of* living organisms need be carried the patient is not infected with

any disease requiring separate treatment, the temperature responses by a satisfactory technic are adequate the reactions fewer and the method materially less dangerous than an inoculation therapy On the other hand it has certain disadvantages, including a rapidly developing immunity on the part of the patient to the proteins of the introduced bacteria, and a consequent somewhat erratic behavior on the part of the fever including the necessity for enormous doses to obtain satisfactory pyrexial peaks. This objection can, however be overcome. As the use of induced malaria becomes more difficult because of the scarcity of quinine, typhoid vaccine because of its accessibility and controllability especially for the isolated case may become more popular The technic and care of patients are somewhat less exacting but technical detail is nonetheless essential, particularly with regard to the timing of the injections and their intravenous, not paravenous or subcutaneous, administration. Unsatisfactory fever levels result from inexperience or the use of interne service without proper supervision. Fever levels in refractory cases can be raised by hot drinks and blanketing and the temptation to overdosage should be resisted.

So far as comparisons with malarial therapy are concerned, they are few for comparatively few of the patients treated by this method in various series seem to have been adequately followed. O'Leary rates it as a useful method of treatment with about 15 per cent fewer complete remissions than malarial therapy but well adapted to use as an adjunct where malaria is contraindicated, has failed due to native or acquired immunity or where a malarial strain cannot be carried and only an occasional case is to be treated. Kemp and Stokes, following the original American study of Knode, Hall, and Gerty used this method of treatment in resistant neurosyphilis in general, and found it fairly effective, very well tolerated, and susceptible of repetition in successive courses. The necessity for enormous doses, as high as 4000 million organisms intravenously is annoying and may sometimes produce shock. Nelson devised the plan of giving two daily injections of the vaccine the first ranging from 25 to 50 million organisms, sufficient to produce slight fever and the second administered two to three hours later at the height of the fever induced by the first injection, ranging from 25 to 60 million organisms. By the use of doses from 20 to 300 million in the first and second injections, fever of 105° and 106° F was obtained where only 102.6° F could be obtained by the old single-injection method, using a small dose. His series was too small to judge of clinical or serological results, but our own impressions are very favorable. Driver and Shaw have reported on 21 cases with pyrexial curves fully equal to anything obtainable with malaria. They regard Nelson's method as an acceptable substitute. Kulchar and Anderson (1937) found typhoid flagellar (H) antigen in divided doses provided a safe, satisfactory method of fever therapy which because of the slight degree of systemic reaction, can be used in the treatment of patients whose physical condition does not permit the use of other forms of nonspecific therapy In a more extended study (118 cases) Kulchar and Card (1941) reaffirmed the value of this form of fever therapy H. A. Solomon and Somkin (1946) have proposed continuous infusion of triple typhoid vaccine suspension as a means of inducing controlled sustained hyperpyrexia.

This method in our experience is applicable to the occasional case and is useful in serologically fast patients and other resistant conditions than neurosyphilis. It is not yet recommended as a substitute where malaria is available. The combination of hyperpyrexia and arsenicals can be very well studied when typhoid-paratyphoid vaccine is used, and there were indications in our series that this combination was more than ordinarily effective.

Other methods of inducing fever by foreign protein in the treatment of neurosyphilis have had comparatively little popularity in this country Dmelcos, a vaccine prepared from the streptobacillus of Ducrey neoaprovitan; Coley's serum pyrifer a B coli derivative yeast suspensions have all been used in addition to tuberculin for the production of therapeutic fever but none has thus far demonstrated distinctive advantages or been followed through a sufficient series to judge of its effectiveness.

Chemical Methods for Inducing Fever.—These have now been practically superseded by the other methods described, and can be referred to in the second edition of this work.

PHYSICAL METHODS OF FEVER INDUCTION

With its famous mechanical know-how and gift for the devising of apparatus, the United States has seen the maximum development of fever induction by mechanical means. In fact, foreign observers have been astonished by the tidal wave of enthusiasm for these technics brought on by the war emergency and have done us the compliment to send their ablest talent to observe our progress. Of mechanically induced fever as the apparatus and technic renders the procedure increasingly safe, controllable and not too uncomfortable for the patient, it may be said that probably the whole future of the use of this agent, elevated body temperature in the treatment of syphilis, will ultimately lie within this field. This, we believe, holds, notwithstanding our present feeling that induced malaria as ordinarily practiced, offers the patient the largest return on the briefest investment of time, trouble, and risk. Of the various available procedures, the same principles should be recognized as were recognizable in the field of fever therapy as a whole decade ago. The methods tend at the start to be esoteric, markedly dependent on adequate institutional set-up and highly specialized equipment which has the tremendous disadvantage, especially when used throughout the wide range of manifestations of the disease, of compelling the concentration of treatment into not always easily accessible centers. On the other hand, as familiarity with the methods and training in its procedure is extended, gradual simplification takes place, and there become available alternative procedures of reasonable safety and effectiveness which are usable under a wide range of circumstances with simpler and less expensive apparatus. The controls placed for example by the Miami Valley Hospital group, on the use of the hypertherm, or air-conditioned cabinet, had a valuable effect in preventing a sudden rise in mortality from mishandling by untrained persons, but such restrictions can hardly be indefinitely continued as wider application, broader medical training and increasingly trained technical personnel develops with use. The allure of the gadget also contributes something to American application of these methods. It is therefore proper to point out at this time that a selection of mechanical temperature-raising procedure is possible, contingent upon circumstances, and availability. The electropyrexial technics, because of their more elaborate equipment and more exacting technic of application, will continue for a time the tool of ultra-experts, but there is no present evidence that their superiority in results is such that they will maintain their place against the competition of the simple air-conditioned cabinet. There will, moreover, particularly under stress of war, be need for methods employable where apparatus and technical specialists are not available, and for such purposes, the bath, the blanket and hot-water bags, and the simple light cradle will be found useful. One of the initial serious draw-backs of a machine that can raise temperature so easily to such unprecedented heights and maintain it at such levels for many hours, is the temptation to overplay the game and to employ far more intensive pyretotherapy than may be proved ultimately either necessary or desirable. There is therefore room for further careful study of what might be called ambulatory technic with less frequent and less elevated sieges of fever. That such methods are usually studied where funds and organization as well as mass of patients are at their lowest rather than their highest, possibly explains the slowness with which their potential value is demonstrated.

One of the great advantages of the induction of high body temperature by mechanical means is its noninterference with intensive chemotherapy. The combination of fever and chemotherapy seems both theoretically and clinically so definitely superior to fever therapy alone and so much more specific than fever induced by another infection or by foreign protein, that the fever-inducing devices which make the best combination with chemotherapy seem likely to hold the field for the future.

It seems likely also, as the result of administrative convenience, that the rapidly increasing importance of pyretotherapy in the treatment of gonorrhea unless replaced by a new drug (penicillin?) will *pari passu*, increase its availability for the treatment of the sister venereal infection, syphilis. This is particularly likely under the pressure of war emergency and may lead ultimately to a condition of centralization of the treatment of venereal disease on a wholesale scale in which large fever-chemotherapy institutes are set up for this purpose alone as in the present Chicago experiment. These will be especially important additions to the treatment facilities of large cities.

BALNEOTHERAPY AS A FEVER INDUCING AGENT

Elevation of temperature by means of the hot bath can be carried out on practically any hospital service with a large tub and a competently trained nurse. The assistance and supervision of the plant and attendants in a physiotherapeutic division is a valuable aid, but where prolonged high temperatures

are to be maintained and chemotherapy simultaneously employed, especially in the management of infectious cases, the venereologic or syphilologic division should assume full responsibility The simplified technic, adapted to ordinary hospital use is summarized from Boak, Warren and Carpenter's contribution below

The experimental background of this method, based on the work of Schamberg and Rule, is discussed in Chapter V Mehrtens and Pouppirt, treated 70 patients, giving 900 baths during period of one and one-half years. The patients ranged in age from seventeen to seventy and included many unpromising risks. While continuous bath equipment is desirable, it is not absolutely necessary Mouth temperatures ranging from 104 to 105° F and even 107° F were obtained by bath of 110° F which was started, for timid patients, at temperature of 105° F The temperature of the bath water was gradually reduced to that of the patient after the desired response was obtained. Temperatures were ordinarily maintained for two hours, sometimes by removing the patient from the bath, wrapping him in hot blankets with hot-water bags, and administering hot liquids by mouth. The authors believe that Hollingsworth poor results were the consequence of insufficiently hot baths and insufficient time at the maximum fever temperature. Patients lose, from 3 to 5 pounds' weight with each bath, which is recovered, under proper dietary management, by the next morning. Most patients end series of fourteen baths with gain of weight. The pulse curve follows normal variations, the blood pressure is reduced in most cases, there were increases of hemoglobin and red cell count occasionally with 2 to 3 per cent increase in reticulocytes. At the lower temperatures the patients were calm and cooperative, at medium temperature (102° 103° F.) very frequently showed signs of restlessness and anxiety and at the higher temperatures became apathetic and later mildly confused. None of these effects was serious. The permeability of the meninges was increased, as shown by the Walter bromide test. Of 11 paretic patients, 2 were able to return to work, 4 showed marked improvement. Marked symptomatic benefit ensued in tabes, particularly in patients with lightning pains, gastric crises, and painful Charcot joints. When given routine antisyphilitic therapy in conjunction with the hot baths, the effects seemed materially improved. Baths may be continued daily for at least six weeks and the patient may still gain in weight and maintain his strength. The studies of Dosmis, *et al.* (1936) and Warren have been previously referred to.

Verbal reports from some of our institutional friends indicate that this method is more feasible and effective than at first appears. It would be desirable to devise methods of controlling weakness, perhaps through the loss of chlorides from sweating One observer mitigated the discomfort of his patients by allowing them to keep one leg, from the knee down, outside the tub.

ELECTRICAL METHODS FOR INDUCING FEVER

Physical.—Two methods have been developed.

The better known of the two methods consists in the passing through the body of the *patient of high-frequency current generated by diathermy apparatus of 4000 to 6000 ma.* capacity Large fenestrated electrodes of special construction are applied to the chest, abdomen and back, the principal problem being to get the necessary amount of current through the patient body without producing burns. In the Cook County Hospital and the Elgin State Hospital, where special technic and facilities were developed, the results were highly satisfactory In addition to the correct application of properly constructed electrodes and sufficiently powerful machine, insulation of the patient ith seven blankets and rubber sheet is necessary The rate of temperature rise in patient depends upon the mass of the patient, current and insulation, and any type can be imitated. Perfect imitations of malarial stage, so far as temperature curve is concerned, can easily be produced. The final temperature of the body overshoots the highest temperature obtained during the operation of the machine, so that it must be cut off before the critical point is reached. Restless and disturbed patients are particularly apt to receive burns, which usually occur around the pelvic girdle, where the body is thinnest. The changes in the blood and body chemistry are those of high fever Neymann (1936) has compiled an excellent table, summarizing the work of all reporters on electropyrexia, with total of 975 cases of dementia paralytica, 260 (27 per cent) *complete remissions, 354 (36 per cent) improved, and 23 dying as the result of treat*ment (2 per cent) Neymann and co-workers tend to minimize the difficulties, which are doubtless minimal under sufficiently expert technical direction. Most of the diathermy cases began to show improvement only after the eighth to the tenth treatment. It is particularly interesting that number of the older cases had been treated with malaria and sodoku without result. Salisbury

and Eichenla b failed t secure results in 17 cases of attempted direct diathermy treatment of the head.

Th second method of producing fever electrically consists in placing the patient in the field of high-frequency oscillating condenser The discovery of the pyrogenic properties of this type of electrical energy as made accidentally in the General Electric Laboratories in Schenectady where Whitney noted that orkmen in the field of high-power short wave radio transmitter developed fever Whitney Carpenter and Page, Carpenter and Boak, and Hinsie, have done preliminary work but the Carpenter Warren group has gone *over completely t the radiant* heat cabinet, giving up the electrical induction of fever There is a marked rise in the local temperature of organs ithin the bodies of experimental animals and Hinsie and Blalock have shown rise of 75 per cent in leukocyte count in the blood. Six months after treatment by thi method.

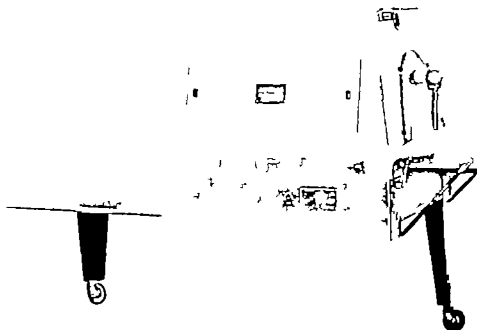


Fig 156 —The hypertherm (closed) (courtesy of Dr H. W Kendell)

17.6 per cent of their patients showed remissions, 33 3 per cent were improved, 38.2 per cent unimproved, and 8 8 per cent dead. The malarial controls gave remissions 19.1 per cent, improved 35.3 per cent, unimproved 30.9 per cent, and dead 14.7 per cent.

Conditioned Air and Radiant Heat Cabinets.—Excellent descriptions and reviews of this type of apparatus, now the most popular means for the mechanical induction of fever have been published by Simpson (1935 1940) Desjardins, Stuhler and Popp (1936) Krusen (1930) Krusen and Elkins (1939) These types of apparatus were the offshoots of attempts to control the arcing and induction of burns by electrical current at points of accumulated sweat The Kettering Hypertherm (Fig 150) utilizes humidified heated

Fig. 157

THE ESSENTIALS OF INTENSIVE PHYSICALLY INDUCED FEVER THERAPY

I. Organization and Personnel.
1. An institutional set up for prolonged sessions, extensive use.
2. A physician in charge who has expert knowledge of every complication and contra-indication.
3. A trained technician or nurse (not less than 4–6 weeks institutional instruction) in constant attendance at the patient's side.
4. For smoothness and comfort for the patient, there must be tact, confidence, consideration and know-how in the attendants.

II. Equipment.
1. Air-conditioned or radiant heat cabinet approved by the Council on Physical Therapy, American Medical Association preferred. Diathermy and other electrical induction methods less safe, more difficult, losing ground. Bath and blankets useful but slow, uncomfortable; may be necessary makeshifts for lower temperatures, shorter sessions.
2. Self-recording electrical rectal thermometer. Mouth axillary and hand-rectal methods makeshift.
3. Blood pressure control.
4. CO_2-oxygen-inhalation equipment (Boothby mask).
5. Antishock equipment (glucose and plasma set, sponge tray, etc.)

III. Patient-Supportive Measures.
1. Instruction, reassurance, comfort (soft mattress, head exposure, body freedom).
2. Adequate preliminary work-up—physical examination and diagnostic survey, functional tests of heart, kidneys, lungs, liver. Blood count, sedimentation rate, urinalysis, electrocardiogram, chest roentgenogram, blood chemistry.
3. Salt replacement—NaCl 8 to 20 Gm. according to fever duration in 3000 to 8000 cc. fluid (iced tea, fruit juices, sweet beverages).
4. Intravenous glucose 5 per cent in 1 per cent salt solution, 1000 cc. if needed.
5. Oxygen with 5 per cent CO_2, inhalation p.r.n.
6. Cold compresses to the head. Light covering of skin surface and prominences.

IV. General Principles.
1. The higher the fever and the longer the session, the greater the risks.
2. The patient must be *observed* (not merely looked at) continuously. Vigilance is of the essence.
3. Contraindications and possible complications should be re-considered with each session, not merely at the outset.
4. *Remember the five 6's*: T 106° P 160, R 60, BP (diastolic under) 60 BUN over 60 (upper limit of blood urea nitrogen). These mark the danger line.

V. Complications. *Death* (vascular collapse shock, heat stroke, cerebral hemorrhage and edema, pulmonary edema, hemorrhage). *Psychic disturbance* (restlessness, dementia). *Convulsions. Headache* during and after. *Nausea and vomiting. Cramps*, abdominal and muscular. *Tetany. Skin*, erythema, herpes, burns (electrical). *Albuminuria.*

VI. Treatment of Complications (Turville and Fetter 1945). *Headache* aspirin. *herpes simplex* compound tincture of benzoin or 5 per cent ammoniated mercury ointment; *local erythema*, protective pads, *nausea and vomiting* 500 cc. 5 per cent glucose in 2 per cent salt solution intravenously followed by 1–2 liters 5 per cent glucose in normal saline solution; *intractable vomiting*, stop. *tetany*, 10 cc. 10 per cent solution calcium gluconate intravenously; O_2–CO inhalation calcium by mouth; *delirium and hysteria*, ¼ grain morphine repeated in two to three hours, reassurance; if persistent, stop; *circulatory collapse* 1–2 liters 5 per cent glucose in normal saline intravenously, small doses epinephrin, caffein sodiobenzoate, or coramine; if not responsive, O_2 inhalation and plasma transfusion. *heat stroke* stop treatment, sprinkle body with warm water ice-water enema 100 to 200 cc. 50 per cent glucose or sucrose solution intravenously; spinal puncture or venesection for *cerebral* or *pulmonary edema* respectively; *convulsions*, sodium amytal intravenously 3.75 to 7.5 grains occasionally hypertonic glucose and lumbar puncture.

"IF IN DOUBT TAKE HIM OUT"

Fig 138.

AMBULATORY FEVER THERAPY

(Exigent, Casual, Substitute)

1 Weekly or semi-weekly sessions.
2. Preferably combined with chemotherapy Give as fever drops toward normal.
3 Aim for six hours over 104 F per daily session, total of fift hours, t 105°
4 Adequate record of each step and finding must be kept.
5 *Easily obtained by cabinet methods.*
6. Other procedure as follows
   (A.) Blanket: 5–10 Gms. salt i 1000–2000 cc. water preceding t hours. Blood pressure, temperature pulse. Wrap in sheet and 2 3 blankets, enclosed in rubber sheet, with hot w ter bags. Force hot sweet drinks; temperature axillary later mouth, q thirty minutes. Electrically wired (waterproofed and insulated!) blankets may be used. Do not wrap. Place above and below Method slow uncomfortable, trying for patient.
   (B.) Blanket and Cradle (after N Epstein) Wrap in bath blankets, large woolen blankets, rubber and canvas sheeting. At start, cradle ("common body frame") with 12 carbon lights is placed over patient. The patient is given no special preparation and is permitted to have breakfast. Long woolen socks are placed upon the feet and legs to the knees. A heavy woolen blanket, a canvas sheet and rubber sheet sufficiently large t cover the entire patient are placed upon the bed. Warmed thin blankets are wrapped around each limb and the trunk of the patient so that no part of the body is uncovered except the face. Seven bath blankets are used. The heavy woolen blanket, the canvas sheet and the rubber sheet are successively brought up and wrapped around the patient. Two more heavy woolen blankets are used, one is placed over the feet and lower half of the body the other is wrapped around the entire body During the treatment the patient may be placed in a semi-sitting position if desired. 100 cc. of hot lemonade (100 F) containing sugar and 0.6 per cent sodium chloride is given at one-half hour intervals. 3–4 liters are given during the treatment. Morphine sulphate gr ¼ nd tropine sulphate, gr $\frac{1}{150}$ are given hypodermically for restlessness and morphine sulphate, gr ¼ may be administered t or three hours later if necessary The oral temperature is taken t least five minutes before hot liquids are given and the pulse is counted at the temple t half hour intervals. The fever is permitted t rise to 40 5° C. (104.9° F) and is maintained between 39 C. (102.2° F) and 40.5° C. (104 9 F.) for six hours. At the conclusion of the febrile period the blankets are removed, a warm alcohol rub and cool drinks are given. The patient requires expert ursing care throughout the period of hyperpyrexia The onset of alarming symptoms such as rise in temperature above 40 5° C. (104.9 F) or of the pulse rate above 150 per minute, tendency toward collapse or the onset of tetany are indications for lowering the temperature or discontinuing the treatment. Loosening the blankets as rule will cause prompt decline in the temperature. Occasionally fanning the body tepid sponges, ice hips by mouth or cold colonic flush must be used t reduce the fever A fall in systolic blood pressure below 80 mm. of mercury should be regarded as sufficient cause t discontinue the treatment. There is an even and gradual rise in oral temperature veraging 0.2° C. per fifteen minutes or 0.8 C. to 1 0 C. per hour. The rectal temperature is 0.3° C–0.5° C higher than the oral temperature A temperature of 39 C. (or 102.2° F) is attained in three t four hours, and 40° C. (or 104 F) i four t five hours. This temperature is then easily maintained for the febrile period. The pulse rarely exceeds 140 per minute and the respirations 28 at the height of the fever The temperature falls t normal in about one hour after conclusion of the treatment. The initial rise in temperature an be greatly accelerated by placing a common lectric body bake over the patient for one to t hours before the rubber sheeting is wrapped round him.
   (C.) Tub (after Bozk, Warren and Carpenter) 2 Gms. salt in 500 cc. water by mouth two hours before and after bath, 2000–4000 cc. fruit juices, tea, t during and after *Bath.* Immerse patient completely p to chin in t b of water t 42° C (107° F) Additional hot ater is added as needed t keep the ater temperature constant t thi level. The w ter should be stirred and mixed, and the temperature of the ter measured at both ends of the tub.

Fig. 148.—Continued.

1. The mouth temperature and pulse are to be measured accurately every five minutes by the clock. When the oral temperature reaches 103° F the patient is to be taken at once from the tub, dried off, wrapped in a dry sheet, and placed on a cot t cool down. Patient can be allowed t walk to the cot, unless dizziness, nausea, or palpitation is present. Duration of session about forty minutes. Note the most critical period is the five-minute period at or near 103° F The temperature will rise rapidly if the patient is left in too long at this level.
2. Blood pressure reading following bath.
3. Take temperature t ice more after patient is out of bath t be certain patient is cooling down.
4. During cooling down process at least t glasses of cold ater (400 cc.) should be ingested, to which salt may be added if water tastes flat.
5. 2 Gms. salt and water to be given one hour after bath.

(D) If the patient feels chilly after the bath, he should be covered as much as necessary for comfort only He may be allowed t sleep for half hour or more, and thereafter may rise and walk about.

(E.) If arsenical therapy is t be used, the injection is given during the cooling off period.

(F) Tub bath procedure may be repeated again after eight hours if desired.

air distributed by fans from a fireproof chamber at the end of the cabinet to the patient lying at rest upon a suitable sponge-rubber or air mattress, completely enclosed under a cabinet cover which can be lifted for adjustments, necessary observation and so forth. Only the head of the patient projects, the neck being enclosed by a sponge rubber collar which is soft, flexible and devoid of constrictive effects The self-recording electrical rectal thermometer is regarded as an essential part of these types of equipment, and fans for cooling the exposed face and head are desirable refinements. The radiant heat cabinet devised by Warren simplifies the equipment by doing away with the air-conditioning and circulating apparatus. It con ists of an essentially similar cabinet, in the top of which are housed five 200-watt Robert Schwartz heating lamps, so arranged that three irradiate the trunk of the patient and two the lower extremities. This type of lamp is chosen because it is a strong emitter of infra-red rays. The lamps are controlled by rheostats, since they deliver more energy than is usually required. Other types of luminous and non luminous heat cabinets have been designed but the prospective purchaser of uch equipment should consult the reports of the Council on Physical Therapy of the American Medical Association which has painstakingly investigated the various available types. While each type of cabinet has its advocates, the evenness and continuity of the fever in the Hypertherm without the necessity at any time for exposing the patient are being stressed, and the relative simplicity efficiency and inexpensiveness of the radiant heat type.

It should be clearly understood that the use of these types of apparatus is not to be regarded as an office procedure at this time that the skill and experience of the medical and technical attendants re of far more importance than the apparatus and that the mere ability to secure the apparatus furnishes no justification whatever for the employment of it in the treatment of disease

Electrically Heated Blankets.—These are rubber-insulated, covered wire-mesh devices similar to electric heating pads which are applied outside of zipper bag completely enclosing the patient. The close confinement is disturbing in proportion t the elevation of temperature sought, as in the case of other blanketing devices, hich limits the usefulness of the method, and thus far no device of this sort has received the pproval of the Council on Physical Therapy (1943)

CHAPTER IX

THE REACTIONS, COMPLICATIONS AND CONTRAINDICATIONS OF TREATMENT FOR SYPHILIS

The Factors in Reaction.—Under the intensive and radically curative régimes made possible by modern syphilological methods no small part of the art of treating syphilis consists, not in the mere administration of doses of this or that, but in the study and prevention of unfavorable reaction, and the minimizing of treatment risks. It is very difficult to escape the tendency to blame the drug exclusively when one encounters a reaction to treatment. The names "arsenic" and "mercury" have been so long associated in our minds with gripes and poisoning that the *post hoc* type of reasoning is inevitable and natural. The tendency must, however be consistently fought by all who wish genuinely to understand the mechanism of treatment reactions. Injurious reaction from faulty preparations is extremely unusual. No small part of the trouble encountered in modern syphilis treatment arises from medical and technical error and from individual and often remediable peculiarities in the patient.

It follows, therefore that the study of the patient's individual reaction to treatment must never be neglected for any system or routine, no matter how authoritative the source. If we decide to push a given method through in the face of contraindications, it should always be with full knowledge of the risks involved and the end to be attained. On the other hand, if we bow too easily to the first indication that the patient is having difficulty with some phases of his treatment, we shall be weak-kneed therapists and have a correspondingly poor aggregate result.

Tracing Reaction Causes.—Because a patient develops jaundice after an arsphenamine has been given or stomatitis after a mercurial, it by no means necessarily follows that the drug is the cause of the reaction. A theory of predisposing as contrasted with exciting causes does excellent service here. Moreover the study of reaction tendencies makes it increasingly clear that all the various drugs employed, but particularly the arsenicals and bismuth, play upon a physical reaction mechanism involving the vascular system, the liver and the kidneys together with the gastro-intestinal tract, in ways which make the effects of combined treatment with two or more drugs often very difficult to interpret. This fact became particularly apparent in the Cooperating Clinic survey of reactions in early syphilis in which it appeared quite definitely that treatment with an arsphenamine alone gave rise to a comparatively trifling number of complications as compared with the effects of combining a heavy metal in the scheme of treatment. The various factors involving a stepping-up of reactivity and a reduction of tolerance are therefore constantly interwoven and make the reacting patient a problem for a high degree of individualization and expert study. Fortunately however there are certain general principles and general measures which have a wide degree of validity in all cases.

The Distinctive Reaction Tendencies Recalled.—Let it be recalled, then that the trivalent arsenicals attack the vascular system and the liver and

through the vascular system the skin. The bone marrow is also more subject to arsenical attack. Pentavalent arsenicals attack the nervous system. The kidney is in general relatively exempt; the gastro-intestinal tract usually only mildly though perhaps disagreeably affected. The heavy metals, because

Fig. 190.

SOME MAJOR AVOIDABLE CAUSES OF REACTION REVIEWED

1. Failure to consider the patient as a whole or to examine in particular for: (a) damage to vital structures; (b) activity of the disease in vital structures; (c) intercurrent disease.
2. "Wassermannism" or "Serologism." Treating for or by the blood test alone.
3. "One system for all," one drug, one size ampule, no weighing of risks against benefits.
4. Failure specifically to consider tolerance in each case.
5. "Taking a crack at it":
   Unfamiliar with the common drugs,
   Or their reactions,
   Or outright contraindications.
6. Experimenting with unfamiliar drugs without previous study.
7. Pamphlet and drug circular syphilology.
8. Arsphenamines without preparatory treatment in syphilis of vital structures, implying:
   Unfamiliarity with therapeutic shock (Herxheimer effect),
   Unfamiliarity with therapeutic paradox ("the fatal cure").
9. Wrong drug for the purpose, e. g., 100 injections × 0.9 Gm. "914" in paresis. Bismuth alone in primary syphilis.
10. Wrong route for the right drug: e. g., bismuth intravenously.
11. "One dose for all." Failure to regard weight, and other standards.
12. The initial overdose.
13. Disregard of cumulative effects, especially heavy metal.
14. Failure to watch the eliminative mechanism: the kidney, the bowel.
15. Rest intervals in early syphilis.
16. Treatment by hearsay.
17. Hurry.
18. Defective drugs or drug containers (a rare cause).
19. Dietary mistakes:
   Full stomach before injection.
   Too much roughage.
   Too much carbohydrate.
   Alcohol.
20. Technical blunders:
   Giving acid "606" for "914."
   Fast injection—"speed shock."
   Improper mixing of neoarsphenamine:
      Imperfect solution.
      Aeration.
      Shaking.
      Standing.
   Failure to pull back on syringe plunger (Fig. 196).
   Injection into inner and lower quadrants (of the buttock).
21. Failure to inquire for, see, or heed warnings of serious reaction, especially from the skin (itching, rash, purpura) before each treatment.

NEVER GIVE A FIRST INJECTION WITHOUT THOUGHT; NEVER GIVE A SECOND WITHOUT KNOWING WHETHER THE FIRST WENT WRONG OR NOT AND WHY

of their mode of introduction, have annoying local effects. They act as depressant protoplasmic poisons instead of tonics, as in the case of the arsphenamines. The gastro-intestinal tract, and particularly the mouth, is the site of many reactive phenomena under heavy-metal therapy. The kidneys in general

Fig. 160.

SOME FUNDAMENTAL FACTS CONCERNING TREATMENT REACTIONS

Based on the major reports in the literature 1920–1943.

1 Some degree of reaction is probably inevitable in effective treatment for syphilis. It is inherent in the composition and metabolism of the drugs.

2. The frequency of complications is influenced greatly by uniformly correct, stable and expert technical preparation and manipulation of drugs, especially in clinics. (Haase and Marshall, Stokes.)

3. All reactivity is increased by the intensive use of heavy metals. With arsphenamine alone, the reactivity is low (38.7 per cent *versus* 56.3 per cent)

4. The patient who has one complication tends to have others.

5. Increasing age of the patient and of the infection influences the incidence of reaction (see p. 306) Dermatitis, jaundice and nitritoids tend to be less frequent in older patients. Gastro-intestinal reactions and pruritus increase in secondary syphilis.

6. The greatest incidence of reaction is between the sixth and the tenth or seventh to fifteenth injection in the arsphenamine series (Cole, Harrison); 75.2 per cent before the tenth, 45 per cent between the first and fifth (Univ of Penna.); with a drop after the twentieth and a rise after the fortieth. A series of from 20 to 40 injections, therefore, brings the patient int a period of minimal rather than maximal reactivity; 5.5 per cent after the twentieth (Univ of Penna.). After the latter figure the risks again increase. Severe reactions may occur early or late, depending on the type of reaction. 87 per cent of crustaceous dermatitis reactions occur less than two months after beginning of treatment (92 per cent follow 1 t 6 arsenical injections) (Waugh and Milovich, 1940) but blood dyscrasias tend to appear late in the course of therapy (Burke 1941)

7 Dosage probably influences the later reactions more than the early ones, grave cutaneous and vascular reactions may follow very small individual and total doses, early and late in treatment, and overdosage leads t many and severe reactions. (Mahrowsky Statistics, Fig 161.)

8. Secondary syphilis, in the aggregate, however is less reactive than primary

9 Early syphilis is less reactive than latent syphilis. (Cole, 15.3 per cent *versus* 19 per cent.)

10. Complications are roughly divisible into major (severe) and minor (mild) as follows: Under major reactions are included aplastic anemia, atrophy of the liver exfoliative dermatitis, jaundice, purpura hemorrhagica, aleukemia hemorrhagica, hemorrhagic encephalopathy severe gastro-intestinal reactions, ocular damage, renal reaction, and death. Under minor reactions are included slight skin eruptions, pruritus, Herxheimer effect, nitritoid reaction, arsenical stomatitis (unassociated with aplastic anemia) For relative frequency see Figs. 161 t 178

11 Continuous treatment causes more minor but no more, if as many major reactions, as the much less effective intermittent treatment.

12. Kidney tolerance is better under continuous tha under intermittent treatment (6.1 *versus* 18.5 per cent reactions) MacF rland showed that the kidney acquires a tolerance of treatment.

13. The aggregate incidence of arsenical reactions is 15.3 per cent of cases (Cole)

14. Arsenical reactions as such are most frequent in ages forty and forty-nine.

15. Of the patients who have had one arsenical complication, nearly two-thirds can cautiously continue treatment. Of those who have had two complications, 25 per cent can continue arsenical treatment (Cole *et al*)

16. Of patients receiving two arsenical treatments, only about 0 per cent were sensitive t both. A change of drug may therefore reduce reaction (For precautions in dermatitis cases see p. 428)

17 Sensitivity to th arsenicals lasts from verage of eight and four-tenths months (Cole 63 cases) t seventeen years (in Burke case)

18. Hemorrhagic encephalopathy affects the young adult nd ha mortality of 30 t 50 per cent. (Cole Harrison, Phelps and Washburn) It causes 50 per cent of treatment death

19. Exfoliativ dermatitis may occur after much or little arsphenamine The factors involved are discussed on pages 216, 253. It causes 23 per cent of deaths.

20. Neoarsphenamine gives rise t more icterus, much or more dermatitis and more severe gastrointestinal reactions than 606. Arsphenamine 606 gives rise t more minor reactions, but only very few more major ones th 914

Fig 160 (Continued)

SOME FUNDAMENTAL FACTS CONCERNING TREATMENT REACTIONS
(Continued)

21 **Sulpharsphenamine** in the United States Navy has nearly as good a reaction record as neoarsphenamine, but this cannot be said of reports from civil practice except when the drug is used in children.

22. **Mapharsen** (an arsenoxide) has an exceptionally low incidence of all types of reaction, especially nitritoid, when used in standard systems of treatment. Under some circumstances it may be tolerated by patients who develop mild reactions to other arsenicals. It is capable however of causing severe reactions and death in intensive systems, from encephalopathy and blood dyscrasias.

23. **Reaction statistics** are much influenced, probably by treatment technic, clinic versus private practice, patient's physical status, diet and nutritional state of the patient, season of the year, patient's nervous state, pregnancy, intercurrent infection, follow-up effort and gradual progress in the perfection of drugs.

are more markedly affected than with the arsenicals, the vascular system less so. The liver, although it is the great toxicity burden-bearer of the body, is definitely less affected by the heavy metals than by the arsenicals. The skin likewise has a relative immunity to heavy metal effect. Mercury and bismuth part company very definitely in reaction-producing qualities, mercury damaging the gastro-intestinal tract and the kidneys, bismuth tending toward the arsphenamines in the greater inclination to affect the vascular system and the liver. It follows thus that in the interpretation of reaction there is a rational tendency to ascribe vascular, hepatic and cutaneous reactions to the arsenical element in treatment and gastro-intestinal (including stomatitis) and renal reaction to the heavy metals. Iodide occupies a curiously nondescript position. Its reactions are mainly the products of gastro-intestinal irritation and of idiosyncratic, quasi-allergic manifestations. The bad taste, the colic and dyspepsia, the acne, coryza are essentially trivial. Only rarely does one meet a reaction to iodide serious enough to cause alarm.

The Morbidity and Mortality of Treatment Reactions.—Knowledge of this field has advanced materially in recent years, although incomplete reporting and differences in statistical interpretation still lead at times to scarcely credible figures. The difference between ambulatory, hospital, and private practice becomes increasingly apparent as one finds himself preponderantly involved in one or the other. Probably the only true reaction statistics are to be obtained from a bed service with patients under constant and long-time control, such as one scarcely obtains outside of isolated communities, penal institutions and with massive arsenotherapy. For practical purposes, however, the general situation is fairly clear and the reactions which escape recording in ambulatory practice tend to be of minor importance. There is, however, much difficulty in distinguishing between avoidable and unavoidable morbidity and mortality. The administration of arsphenamine to a patient with an obvious contraindication may result promptly in death, not from the arsphenamine as such, but from its improper use. Such complications as pneumonia developing when the drug is given at the onset of an acute bronchitis; death from rupture of an aneurysm or from angina pectoris if the treatment is begun without proper preparation; exfoliative dermatitis following a repetition of treatment in a patient who gives obvious warning signs that were overlooked; aplastic anemia and fatal purpura developing under the same circumstances, death from a cerebral accident, if arsphenamine is given in a large dose to a patient with an acute syphilitic involvement of the brain (Herxheimer effect) cannot fairly be laid at the door of the drug. Such treatment reactions are not drug reactions in any proper sense, yet they are only too readily used by antagonists to discredit even the intelligent use of modern method.

(a) **The Statistical Summaries.**—Current knowledge of the incidence of reaction is summarized in a series of Figs. 161 to 172. These at first are fairly representative of present-day American

as is inevitable in ambulatory practice, number of the mild reactions. The incidence of mild reactions as such, for Stokes' Mayo Clinic service was from 22 to 26 per cent for arsphenamine (606) and 2 to 8 per cent for neoarsphenamine. The chief serious reactions are gastro-intestinal, hepatic injuries, and dermatitis, the chief minor reactions, vascular and cutaneous. Recall that these patients were on combined treatment and that there was no hemorrhagic encephalitis and only one fatality in the group. Fig. 102 shows the incidence of reported reactions to Mapharsen. The absence of nitritoid reactions and the scant number of cases of exfoliative dermatitis are noteworthy.

Serious and Fatal Reactions.—Recent studies of the severe and fatal reactions to the arsenicals based on standard systems of therapy have emphasized in addition to hemorrhagic encephalopathy as the chief cause of death from

Fig. 103.

Deaths and severe reactions following the administration of 1,355,058 doses of neoarsphenamine, 1925–41; ratio of deaths and severe reactions to doses

	Death		Severe reactions		Deaths and severe reactions	
	Number	Ratio to doses, 1 to	Number	Ratio to doses, 1 to –	Number	Ratio to doses, 1 to
Hemorrhagic encephalitis	16	84,691	1	1,355,058	17	79,709
Arsenical dermatitis	13	104,235	201	6,744	214	6,332
Vasomotor phenomena	6	225,843	57	23,773	63	21,509
Blood dyscrasias	8	169,382	20	67,753	28	48,395
Acute renal damage	2	677,529	5	271,012	7	193,580
Acute yellow atrophy of the liver	2	677,529	0		2	677,529
Vascular damage (probable renal hemorrhage)	1	1,355,058	0		1	1,355,058
Liver damage	1	1,355,058	24	56,461	25	54,202
Jarisch-Herxheimer	0		2	677,529	2	677,529
Gastro-intestinal	0		5	271,012	5	271,012
Polyneuritis	0		1	1,355,058	1	1,355,058
Borderline hemorrhagic encephalitis	0		1	1,355,058	1	1,355,058
Arsenical neuritis	0		1	1,355,058	1	1,355,058
Optic neuritis	0		1	1,355,058	1	1,355,058
Classification undetermined	1	1,355,058	0		1	1,355,058
Total	50	27,101	319	4,248	369	3,672

From Stephenson, Chambers and Anderson, U. S. Nav. Med. Bull. 41: 230, 1943.

these compounds (Cologne Commission 1920 and U. S. Navy 1919–1927; Phelps Cooperative Clinical Group, 1933) the cutaneous, hepatic and "shock" reactions as causes of death (Hahn 1941); Stephenson, Chambers and Anderson (1943) (Fig. 103). In the case of intensive (massive) arsenotherapy hemorrhagic encephalopathy is still the outstanding obstacle in the popularization of the "five day" or other foreshortened treatment schemes (Leifer, Chargin, Hyman (1941); Thomas and Wexler (1941) and Thomas, Wexler and Dattner (1942).) Acute yellow atrophy of the liver accounted for 20 of the 45 arsenical deaths in the Johns Hopkins Hospital series (Hahn (1941).) Dermatitis was second, causing 8 of the fatalities. The introduction of mapharsen has materially reduced the incidence of cutaneous reaction (Epstein (1941)) to a

fraction of that caused by other trivalent arsenicals. Although factors involved in the production of arsenical reactions will be discussed later special attention should be paid to the tendency for certain drugs to induce severe or fatal reactions (Cole, Burke (1941))

Mild Reactions to the Trivalent Arsenicals.—These are detailed in Fig 165 Those for the Mayo Clinic probably present the truer picture. Ireland's study from the University of Pennsylvania (left-hand column, Fig 165) shows quite clearly how reports of lesser reactions such as headache, mild diarrhea, fever and subjective complaints fade out of the statistics of an ambulatory service On a service conducted by experienced operators and

Fig. 164.

PROPORTION OF REACTIONS OF VARIOUS TYPES, 1929–41 TO THE ARSENICALS*

Classification.	Number of reactions.	Per cent of total reactions.
Vasomotor phenomena	353	40 07
Arsenical dermatitis	296	33 14
Blood dyscrasias.	44	4 99
Liver damage	40	4 54
Table reactions	25	2 83
Jarisch-Herxheimer	23	2 61
Reactions of minor importance	22	2 50
Gastro-intestinal.	18	2 04
Hemorrhagic encephalitis	9	1 02
Optic neuritis.	3	34
Arsenical neuritis.	2	23
Acute renal damage.	2	23
Border line, hemorrhagic encephalitis	1	11
Liver damage (doubtful reaction)	1	11
Vascular damage (probable adrenal hemorrhage)	1	11
Total	881	100 00

The Cologne Commission in 1920 reported:

Encephalitis causes	60 per cent of deaths.
Dermatitis causes	25
Liver injury (jaundice)	10
Hemorrhagic reaction	5
Myelitis	5

From Stephenson, Chambers and Anderson, U. S. Nav. Med. Bull. 40 1018, 1942.

technicians under constant experienced control and supervision the nitritoid crisis practically disappears as a significant reaction but the proportion immediately rises, under the pressure hurry and more casual conduct of an ambulatory or dispensary clinic Use of mapharsen, as previously stated, avoids the nitritoid crisis. Gastro-intestinal disturbance rates very much the same in both types of clinic and is one of the abiding annoyances and difficulties of the modern treatment of syphilis, responsible for an unknown amount of disaffection, lapse, and noncooperation on the part of patients.

That in the incidence of mild as contrasted with severe reactions the ambulatory clinic is not necessarily at a disadvantage is indicated by Ireland

Fig. 165

COMPARISON OF TYPES OF MILD REACTION TO "606" AND "914"

Reaction	University of Pennsylvania[1] per cent of reactions	Mayo Clinic 1919[2] Number "606"	Number "914"	Per cent of total number of injections "606"	Per cent of total number of injections "914"	Per cent of total number of reactions "606"	Per cent of total number of reactions "914"
Nausea and vomiting	70.0	897	30	19.5	4.0	74.5	51.7
Headache	0.8	366	15	7.9	2.0	30.4	25.8
Diarrhea	0.8	116	4	2.5	0.5	9.6	6.8
Fever		70	3	1.5	0.4	5.8	5.1
Nitritoid crisis	14.0	59		1.2		4.9	
Arm (technical)		56	1	1.2	0.1	4.6	1.7
Chill	6.3	54	3	1.1	0.4	4.4	5.1
Abdominal pain		41	3	0.8	0.4	3.4	5.1
Backache		34	1	0.7	0.1	2.8	1.7
Flush		18	2	0.4	0.2	1.5	3.4
Leg pains		11	1	0.2	0.1	0.9	1.7
Dizziness		15	1	0.3	0.1	1.2	1.7
Skin (mild)	2.0	6	0	0.1	0	0.5	0
Miscellaneous		26	0	0.5	0	2.1	0

[1] Ambulatory
[2] Bed service.
Compare first and last columns, recalling that they represent different types of service.

summary of our University of Pennsylvania experience as compared in the tables relating to specific serious reactions (Figs 167–170)

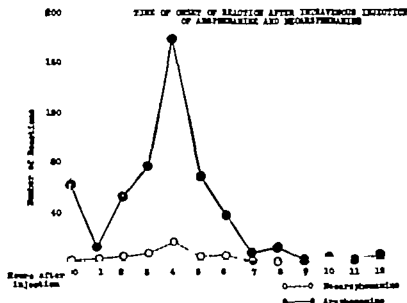


Fig. 166.

Time of Onset of Reaction After Arsphenamine and Neoarsphenamine.—The chart in Fig 166 gives the time of onset of milder types of reaction from Mayo Clinic experience

Ambulatory versus Bed Care After Arsphenamine Treatment.—Undoubtedly when dealing with difficult material, as at the Mayo Clinic one possesses definite advantage in the ability

Fig. 167

DERMATITIS EXFOLIATIVA AFTER THE ARSENICALS

Year	Author or source	Number of injections.	Number of cases treated.	Incidence by injections.	Incidence by cases.
Published 1920	Meirowsky statistics.	215,780		1–5703	
Published 1921	Moore and Keidel.	47,000		1–4272	
1921	Schamberg.	12,000		1–6000	
1916–1921	Stokes and Cathcart.	43,000		1–3583	
Published 1922	D Lees.	56,100	4,800	1–1803	1–475
Published 1940	Harrison.		39,877		1–106
1921–1931	Cole.	78,330	1,218	1–4897	1–73
1928–1931	Ireland (Univ. of Penna.).	53,000	2,100	1–4800	1–665
1910–1928	Cooperative Clinical Group	177,300	6,810	1–1270	
1933–1936 ("606")	Waugh and Milovich.	34,780	3,030	1–1512	1–131
Published 1941 Mapharsen	Epstein.	92,837		1–92,837	
Published 1942 Mapharsen	Levin and Keddie	240,811	12,789	1–15,051	1–801
1935–1941 Published 1943 Neoarsphenamine	Stephenson, Chambers and Anderson.	1,555,838		1–6,532	
5-day intravenous drip Published 1940	Chargin, *et al.*		111 Neoarsphenamine 298 Mapharsen		1–111 0

THE DEATH RATE FROM DERMATITIS IS 1 IN 15,000 TO 1 IN 22,000 INJECTIONS

to hospitalize patients on whom one expects to carry out intensive methods. To the objection to out-patient statistics occasionally offered, that reacting patients go elsewhere and are never

heard from, we would interpose the personal belief that while this is true of mild reactions, one *hears very promptly in one way or another from every serious reaction for which an ambulatory* service is responsible. This is not true of the practice of the private physician, in our experience, for he may lose his patient, especially if part-pay or semi-indigent, to the hospital in the event of serious trouble without hearing anything further of the case.

Incidence of the Serious Complications—Dermatitis, Jaundice, Encephalopathy, Blood Dyscrasias.—Exfoliative dermatitis is with good reason one of the most dreaded complications of modern antisyphilitic treatment. Figure 167 summarizes an extended experience in which the statistical interpretations must vary somewhat on the basis of degree of severity of the cutaneous reactions. The unusually low incidence of dermatitis due to neoarsphenamine is demonstrated by these data. The striking difference in the incidence of jaundice in various reports is apparent (Fig. 167).

Fig. 168.

CASE INCIDENCE OF JAUNDICE

Year	Total number of cases.	Number jaundice cases.	Incidence	Remarks.	Source
1925–31	2100	12	1 175	All types of syphilis.	Univ. of Penna. (Ireland).
1921–31	1212	20	1– 60	Early and latent.	Cole
1931	434	31	1 14	Early syphilis.	Cannon and Karelitz.
1916–29	3244	76	1– 43	Early syphilis only	Cooperating clinics.
1923–33	4120	56	1 74	All types of syphilis with jaundice	Wile and Sams.
1919–34	18,250	158	1–116	Various types of syphilis.	Soffer
Published 1935	7160	21	1 341		Rajam.
1929–33	5196	100	1 52	Various types of syphilis.	Lane
1932–39	6114	100	1 62	Various types of syphilis.	Gott and Doyle.

HEPATIC INJURIES "CAUSE" 10 PER CENT OF DEATHS

The epidemic factor involved is discussed on p. 249. *Hemorrhagic encephalopathy* is extremely variable in its onset and the comparatively low incidence of hemorrhagic encephalitis in Stokes' experience may be a matter of good fortune. That two clinics using preponderantly "606" (Cole and Stokes) have so low an incidence of the complication due to the drug, while a few injections of sulpharsphenamine in Cole's clinic yield 4 cases, and in the Navy none, argues for the entirely erratic character of the reaction or its association with special brands of drugs. When neoarsphenamine is employed in standard systems of treatment this reaction is rare. Aplastic anemia, only recently appreciated in this country, together with its purpuric and hemorrhagic accompaniments as a phase of arsphenamine reaction, can only be summarized from the limited knowledge available as in Fig. 168. The work of the late Dr. Burke (1931) of the Whitechapel Clinic is decisive evidence of sulpharsphenamine as the predominating factor in the production of this reaction since

Fig. 169.

JAUNDICE AFTER THE ARSENICALS

Year	Source.	Number of injections.	Number of cases.	Injection incidence	Remarks.
1920	Meirowsky et statis-tics.	225,730	43	1–5260	"606"—1–8100 "914 —1–6361
1921–31	Cole.	78,330	20	1 3917	1 f tal case.

all of his thirteen cases of blood dyscrasias had received this preparation. There were no cases in patient treated with other arsenicals. Blood dyscrasias have also been noted after mapharsen treatment Levin and Keidlie (1019) collected report of five mild reactions (three purpura, tw

Fig. 170.

HEMORRHAGIC ENCEPHALOPATHY AFTER THE ARSENICALS

Year.	Author or source.	Number of injec-tions.	Number of cases.	Incidence.	Remarks.
1916–1924	Stokes (Mayo Clinic)	63,000	1	1–63,000	56,000 "606" 7000 "914
1919–1927	Phelps, U S. Navy	185,200	18	1 3,533 1 12,880	17 767 inj "606 167 142 inj. "914.
1921 1931	Cole.	78,300	6	1–13,038	4 due t sulpharsphena-mine
1925–1932	Ireland (Univ of Penna)	30,000	0	0	Preponderantly 606. \ sulpharsphenamine.
1936	Glaser Imerman and Imerman (Literature)	1,108,778	189	1–58,700	Arsphenamine compounds
1933–1940	Baehr Chargin, Leifer et al.	304 patients	2	1–167 patients	Massive Arsenotherapy
1918–1940	Hahn (Johns Hopkins)	270,000	2	1 135,000	
1925–1941	U. S. Navy	1,355,038	17	1–79,700	Neoarsphenamine.
Published 1942	Thomas, Wexler Dattner	764 patients	8	1.05 per cent patients	Mapharsen. Intensive syringe technic with or without fever

ENCEPHALOPATHY CAUSES 50 TO 60 PER CENT OF DEATHS

unspecified) and three fatalities from blood dyscrasias, tw from aplastic anemia and one from agranulocytosis.

Comparisons of Arsenicals on the Score of Reaction-producing Qualities.—While the U S Navy experience (Fig 172) the Meirowsky and other statistics

tend to indicate that arsphenamine is from two to five times as reaction-producing as neoarsphenamine from the Cooperative Group study of early

Fig. 171

APLASTIC ANEMIA AFTER THE ARSENICALS
(Analysis by Stephens)

Total reported cases in this series.	Due t neoarsphenamine	Due to arsphenamine	Due t sulpharsphenamine.	Due t diarsenol.
47	27	10	8	2

1 Undoubtedly many unreported cases.
2. The actual frequency unknown and probably dependent on the drugs used. The proportion under "914 is probably low considering the enormous use of the drug under sulpharsphenamine high.
3. Mortality 50 per cent (Farley Burke, 1941)

APLASTIC ANEMIA CAUSES 5 PER CENT OF DEATHS

syphilis it appeared that the proportion of serious to total reactions caused by the two drugs was very similar 48 8 per cent for arsphenamine 606" and 45 4 per cent for neoarsphenamine (914)

GENERAL CONDITIONS AFFECTING REACTION

Age, Sex, Race.—The majority of reactions occur in the age groups in which intolerance of the drugs due t functional impairment of advancing years is t be expected. A partition of reaction incidence between youth and age was observed by the Cooperat ve Clinical Group (1933) which found that there as an increased incidence of mild reaction in the age groups fifteen t nineteen and twenty to twenty four consisting especially of gastro-intestinal and nitritoid reactions. As the age of the patient increased, mild reactions showed tendency t decrease, but severe reactions tended t increase in frequency This as especially true for crustaceous dermatitis (except in the fifteen to nineteen age group) and icterus, which rose from incidence of 0.5 per cent in the age group fifteen t nineteen t 1 6 per cent in the age group forty five to forty-nine Classifying reactivity by type of syphilitic involvement present confirmed these findings. Cole and his associates (1931) found that in older individuals treated with arsphenamine, more icterus was seen than among younger patients. Skin eruptive reactions were more frequent below thirty-five; pruritus above thirty-five. Nitritoid reactions were observed more frequently after this age. In contrast ith the earlier Cooperative Clinical Group findings, severe crustaceous dermatitis was observed almost entirely before the age of thirty-five. Hemorrhagic encephalitis as found by Cole and his associates t occur more frequently in young adulthood. The Cooperative Clinical Group found that mild arsenical reactions were twice as frequent in females as in males *in both colored and hit races; while severe reactions were seen more frequently in hites* without regard t sex. Cole and co-workers showed, furthermore, that whit omen are more reactive than Negro women. Waugh and Milovich (1940), reporting the experience of the Hot Springs treatment center of the United States Public Health Service found that there were 2.47 severe reactions per 1000 arsenical injections among the men, and 2.50 among the omen. The incidence was higher for whit men than colored men, but was higher for colored women than for white women. The single case of acute yellow trophy of the liver observed t Hot Springs occurred in a whit man, and the single case of agranulocytopenia with angina occurred in hite oman with secondary syphilis. These observers found 1 83 icterus reactions per 1000 arsenical injections among the men, and 1 14 among the omen, and no difference in the incidence of icterus as bet een whit and colored patients. Crustaceous exfoliative dermatitis was more the twice as common among omen as among men, and about the same for the hit and colored races. They found, furthermore that this reaction was almost t ice as common among hite

Fig. 178.

ANALYSIS OF REACTIONS TO ARSENICALS

U. S. Navy 1925–1941 *Total Injections 1,792,383*

(Adapted from Stephenson, Chambers and Anderson; U. S. Nav. Med. Bull. 40: 1015, 1942)

	Number of doses adminis-tered	Reactions				Ratio of reactions to doses 1 : —	Ratio of deaths to doses 1 : —
		Mild	Severe	Fatal	Total		
Acetarsone (First used 1932)	971	1	0	0	1	971	0
Arsphenamine	41,568	27	14	1	42	990	41,568
Bismarsen (First used 1929)	3,091	0	0	0	0	0	0
Mapharsen (First used 1936)	188,383	35	14	1	50	3,774	188,383
Neoarsphenamine	1,333,038	650	313	20	983	1,356	57 101
Silver arsphenamine (First used 1931)	886	0	1	0	1	886	0
Sulfarsphenamine	30,834	17	8	0	25	1 233	0
Tryparsamide	71 100	3	1	0	4	17 775	0
Total.	1,794,383	713	339	54	1 118	1,605	33 169

A cerebral hemorrhage following the administration of mapharsen.

women as among whit men, and four times more common among colored women than colored men. While the United States Naval statistics (1933–1941) cannot be used for comparative purposes here, the generally accepted idea that women are more reactive than men may to some extent account for the low incidence of reaction in the N val statistics which concern men, and young men at that. The rôle of pregnancy and other factors explaining the apparently increased incidence of treatment reactions to the arsenical in women will be presently discussed.

Rajam (1935) reported his experience with reactions and complications in the course of administration of 24,530 doses of neoarsphenamine to 7180 East Indians with syphilis. His statement that this race does not tolerate neoarsphenamine is well borne out by his figures; dermatitis was produced in 1 of each 120 patients treated, an incidence of 1 to 147 for men and 1 t 83 for women. The individual dose of neoarsphenamine never exceeded 0.3 Gm., yet there was 1 case of dermatitis for each 431 injections; 1 to 514 for the men and 1 to 204 for the women. There were 3 deaths. Jaundice, however was less than half as common, but in this series hemorrhagic encephalitis developed in 6 cases. In his masterly study of blood dyscrasias in the treatment of venereal diseases, the late E. T Burke (1941) found that approximately 0.5 per cent of women patients and 0.3 per cent of male patients in his Whitechapel series (1934–38) developed blood dyscrasias. Burke found sulfarsphenamine to be the common factor in all of his cases, but does not state whether more men or more women were treated with this drug

In connection with the effect of race, Sampson and Latven (1936) showed that there is definite and constant difference in the tolerance to neoarsphenamine of albino rats from different colonies or racial strains. It is apparent from their experiments that it is not possible to make a significant comparison of toxicity among samples of neoarsphenamine when rats from different strains are used.

Relation of Number of Treatments and of Dosage to the Frequency of Arsenical Complications.—There is little doubt that patients may acquire extraordinary tolerance t the arsenicals, as exemplified by the remarkable case of Photinos (1930) in which woman patient was given total of 191 Gm. of neoarsphenamine in 230 injections of which 190 were 0.9 Gm. each, during period of six years. This probably parallels the improvement in elimination shown by Underhill for the arsphenamines and Hanzlik for bismuth. As general rule, the percentage of persons having reaction rises from the sixth to the tenth injection, and then remains more or less stationary up t the sixteenth to twentieth injections. From this point there is further rise, which then declines t low point between the thirty-first and the thirty-fifth injection. Harrison (1930) and Cole and his coworkers (1931) have both observed severe reactions often from the seventh to the fifteenth dose. The Cooperative Clinical Group (1933) found that reactions either of the mild or severe type occurred with the greatest frequency during the first course of treatment, and dropped off gradually ith each succeeding course. Waugh and Milovich (1940) found that 87 per cent of the crustaceous dermatitis reactions occurred less than 2 months after the beginning of treatment. T enty-tw per cent followed 1 to 6 arsenical injections. In the Cooperative Clinical Group material 67 per cent of the crustaceous dermatitis manifested itself before the second month of treatment, 53 per cent following 1 t 6 injections, and 14 per cent following 7 to 12 injections. In Waugh and Milovich series, men received an verage of 11 injections of arsphenamine and the women 13. Burke (1941) believed from his experience that postarsphenamine bood dyscrasia is unrelated to dosage but that it tends to appear late in the course of treat ment. Our experience corresponds to that of Burke. It is probable that in this and some other types of reaction (g. hepatic) subthreshold injury begins long before the symptomatic reaction appears and can be detected by ppropriate tests (e. g blood smears and counts, icterus index).

Ireland, reviewing University of Pennsylvania experience, found that 75 per cent of reactions occurred before the tenth injection, 43 per cent between the first and fifth, and only 5.5 per cent after the twentieth injection. It is, of course, quite possible that the absolut validity of these statistics is impaired by the tendency of reacting patients to disappear from the records of clinics, but they at least represent everyday clinical expectation. Reactions involving high degree of individual idiosyncrasy vary enormously in their time of onset. Hemorrhagic encephalopathy tends t appear early and Cathcart and Stokes study of exfoliative dermatitis under conditions of hospital control found that most of the reactions occurred on small individual and total doses and in 6 cases out of 33 following the first injection of an arsenical.

Effect of the Type of Arsenical Drug on Reaction.—Sulzberger and Simon (1931) noted in connection with the differing qualities of various lots and brands of neoarsphenamine that there was varying sensitizing proclivity in man as well as in animals, for the various drugs. Cole and his associates (1931), in discussing the comparative number of complications among patients treated with arsphenamine and those treated with neoarsphenamine, found little or no difference in the number of reactions as between the two drugs (15 per cent reaction for arsphenamine and 16.7 per cent for neoarsphenamine)

Mapharsen (arsenoxide) it will be recalled, has as one of its strongest appeals and recommendations an exceptionally low incidence of reaction. Epstein (1941), compiling data from 92,000 mapharsen injections from his own experience and the literature found skin reactions, including exfoliative dermatitis, from one-half to one-third or even only one-sixth as frequent as with the other arsenicals. This was especially true of exfoliative dermatitis.

In common with Appel (1937), Jordon and Traenkle (1937), Cole and Palmer (1937), Astrachan and Wise (1938) Epstein (1941) therefore recommends the use of mapharsen in patients intolerant t other arsenicals He suggests, in view of the experience of Parsons (1937) Foerster and his associates (1935–37) Kalchar and Barnett (1936), and Marshall (1937) all of whom reported recurrences of crustaceous dermatitis after the intravenous injection of mapharsen or pruritus and erythema after such an event, that patch tests be used before the administration of mapharsen to previously dermatitic patients. Fatalities to mapharsen are extremely rare. Mention has already been made of the lessened toxicity of the mapharsen when used in the continuous intravenous drip method of massive arsenotherapy as compared with neoarsphenamine On the basis of lessened toxicity Rein and Wise (1939) have found mapharsen convenient medication for treatment of syphilis in office practice. In addition mapharsen has been advocated, contrary to our considered opinion unless under expert direction, as a substitution product for neoarsphenamine and other arsenical drugs in various of the severe reactions. A summary of the reactions to mapharsen is given in Fig. 108. Acetyl-glycarsenobenzene (sols-salvarsan) has been mentioned previously along with thio-arsene as drugs which have been abandoned in this country because of high incidence of reaction. Triodarsen s reaction incidence is relatively high for adults, though Glynn and Villa (1939) employing this drug in congenital syphilis, reported it well tolerated by intravenous and intramuscular routes. Bismarsen (bismuth arsphenamine sulfonate) has low incidence of reaction and in selected cases can be used as substitute for other arsenicals t which the patient is reactive. The incidence of hematopoietic accidents is low though few recent cases have been reported. Sulpharsphenamine, silver arsphenamine, neoarsphenamine and arsphenamine have been adequately discussed previously

Diet, Nutritional State Social Conditions, as Factors Influencing the Occurrence of Arsenical Reaction.—In the past decade much progress both clinically and experimentally has been made on the effect of diet and other nutritional states on the background of arsenical reaction. There have of course, been impressions that starvation, impaired nutritional states induced by the blockade in the First World War poverty and other factors predisposed patients t treatment reactions from the arsenicals. Müller insisted that bismuth tolerance in the German people was affected by starvation during the First World War Scholl (1942) ascribed w ve of arsenical dermatitis in 1940–41 to the avitaminosis that tends t prevail in the population during February March and April. Stümpke (1941) credited conditions produced by World War II with the observed increase in arsenical reactions in present-day Germany including the influence of the nutritional state, excessive fatigue, and nervous and mental conditions resulting from the War It is now clear however from studies beginning with that of Craven (1931) substantiated by Schifrin (1936) and recently further confirmed by Messinger and Hawkins (1940), that for the liver at least, diet plays major rôle in the prevention of damage by the arsphenamines. Craven showed that dogs on high fat and high nitrogen diet obtained maximum protection against liver injury resulting from the administration of arsphenamine. Of these two diets, Craven found that the former was more advantageous. A high carbohydrate diet, on the other hand, led to maximum susceptibility t liver injury caused by arsphenamine. He also indicated that starvation is an important factor predisposing toward liver injury caused by the arsphenamines. Cystine added to the diet or given intravenously did not increase the protective action of carbohydrate diet. Schifrin came to much the same conclusion as Craven, with reference to the failure of carbohydrate diets to protect the liver against injury from arsphenamine, even when large amount of glycogen was demonstrable in the liver He found, however in contrast to Craven, that high fat diet also left the liver sensitive t the ill-effects of arsphenamine but that diet rich in albumin was the most effective in preventing liver injury by this agent. Bearman (1934) using rats instead of dogs, could not confirm or disprove the contentions of either Schifrin or Craven. In 1940, Messinger and Hawkins found protein to be most effective in protecting dogs against arsphenamine liver injury On protein diet the liver injury was trivial and promptly repaired. They however found carbohydrat diet also beneficial but not as uniformly protective, and liver injury following this latter diet, hen it occurred, seemed more severe. Fat proved to be deleterious and the fat-fed arsphenamine-treated dogs showed markedly progressive jaundice, severe liver injury and intoxication to the point of death

Sulzberger working with Mayer Simon (1934) and others, on experiments with arsphenamine sensitization in guinea-pigs, found that guinea-pigs could be sensitized by intradermal injections of neoarsphenamine with great ease and regularity in Breslau, Germany Boston, Mass.;

Zurich, Switzerland; Odessa, Russia and Ottawa, Ontario. But with the same technique when fed on New York fodder it was practically impossible to sensitize New York guinea-pigs in New York City Sulzberger and Simon believed the cause of this variation in susceptibility t sensitization was not racial or constitutional, for New York guinea-pigs when transported to Breslau and Zurich could there be sensitized with ease Sulzberger and Mayer believed that green fodder (alkaline ash) inhibited and *dry fodder fa ored sensitization Further observations* reported by Sulzberger and Simon suggested that different lots of neoarsphenamine may have been factors in varying sensitizing effects as measured by so-called sensitization index in men as well as in animals. They believe that this index is independent of the actual toxicity of the arsenical as such.

In the past seven years beginning with the experimental work of Sulzberger and Oser (1934) there has been much interest in the question of relationship of vitamin C (cevitamic acid) t various types of sensitivity The problem has been studied by number of workers in connection ith rsenic sensitivity in animals and in man. Certain of these investigators found that vitamin C, administered by various routes, helped to prevent reaction to arsenicals while certain others have not been so convinced of the value of this vitamin as reaction inhibitor Durel (1937) fur thermore believed that using vitamin C in solvents for arsenicals reduced the therapeutic effectiveness of the drugs. This was denied by Dainow (1932 39) and partially by Cormia. This subject is in such stat of flux that it is impossible t the moment to say definitely whether vitamin C, administered orally or by parenteral route, has any significance in the reduction of arsphenamine reactivity On the other hand, there is accumulating vidence to suggest that such relation does exist, insofar as the use of vitamin C-containing solvents for neoarsphenamine administration has proven effective in reducing neoarsphenamine toxicity Furthermore, Cormia (1941) presented convincing vidence of the influence of vitamin C in arsphenamine sensitiveness, by giving 6 patients who had recovered from definite arsphenamine dermatitis, massive doses of vitamin C (500 mg. intravenously daily for seven days) After a cautious intravenous test with minute doses of the same brand of arsenical which had produced the cutaneous reaction, 5 of the 6 patients were eventually able to take full doses of the arsphenamine without further cutaneous reaction The patch test, previously positive, became negative in 3 of 4 patients subsequently tested. Cormia *kept his patients' vitamin C levels high by daily oral administration of 100 t 200 mg of the* vitamin. Abt and his associates (1940–1942) have attempted to desensitize patients t arsenicals by building up and maintaining their plasma ascorbic acid level at optional range. Their observa tions clearly indicate that vitamin C definitely counteracts the toxic action of neoarsphenamine and mapharsen in man. They showed that ascorbic acid prevents oxidation of arsenical solutions left in contact with air They further developed method which demonstrates that typical cutaneous reactions to neoarsphenamine in the majority of hypersensitive patients can be completely prevented by the addition of a sufficient amount of the ascorbic acid to the neoarsphenamine solution used for patch testing Recently Beerman, Pariser and Wammock (1945) successfully employed methylglucamine ascorbat solvent for reduction of mild arsenical reactions. Variations in vitamin A content of fodder do not pparently play role in intracutaneous sensitization of guinea-pigs to arsphenamine (Trei, 1940)

A tempting theory of the effect of vitamin C on arsenical reactions involves its apparent influence upon the allergic state, as suggested for example by Holmes and Alexander report (Science, November 27 1942) on the striking effect proportional to mass of dose of vitamin C on the arrest of hay fever This conception ould bear out Cormia apparent demonstration that sufficiently large doses of the vitamin given intravenously to maintain the blood level have marked anti-allergic effect, and hence in accordance with our previous discussion, could be ex pected to affect the incidence of arsphenamine sensitiveness and dermatitis, the former as ind cated by the patch-test discussed by Abt.

Wien (1938) also made study with large numbers of mice, to see the effects of simple varia tions in an ordinary laboratory diet on resistance of mice to mercurochrome and neoarsphena mine. His results confirmed the belief that in mice the toxicity of the drug is among other things dependent on diet. He was able t demonstrate for example that in toxicity determinations of neoarsphenamine preparations made on various diets, different values ere obtained for the ver age lethal dose under different diets He suggested that toxicity determinations for arsphenamine preparations be made simultaneously ith the standard brands.

There are additional reasons for believing that a high carbohydrate intake is unfavorable to the patient undergoing arsphenamine treatment. In the first place, its well-known tendency to exaggerate seborrheic processes increases the seborrheic predisposition toward exfoliative dermatitis. It contributes, moreover to pyogenic complications both in exfoliative dermatitis

and iodism. It promotes dental decay and to this extent negates the effect of mouth prophylaxis. There are, therefore, a number of reasons for believing that a high carbohydrate diet (incidentally particularly common among the poor) a low fat intake such as occurs in periods of blockade as in Germany during the War and fasting such as is a concomitant both of poverty and indisposition, may all work together to increase the tendency to arsenical reaction.

Seasonal Influences on Arsenical Reactivity—Reactivity especially serious, tends to occur in waves over periods of years and with a tendency to seasonal peaks The winter and early spring months seem to yield the higher incidence especially of liver and skin reactions.

Mention has already been made of Sulzberger's, Mayer and their associates work on the effect of differing geographic areas as factors in the sensitization proclivities of various arsenical drugs. This work, to some extent, is corroborated from the standpoint of the effect of seasons by the studies of Akiyama and his associates who found among the reactions occurring in 2016 cases treated with arsphenamine in the period from 1921 to 1937 that the arsphenamine exanthemata were seen most frequently in January and June.

The Cooperative Clinical Group (1935) made observations of the effect of different years in which the treatment was given on the incidence of treatment reactions to the arsenicals. The rate per 1000 injections for severe reactions dropped in all the clinics progressively from 1920 to 1931 inclusive. On the other hand, with mild reaction, after a great increase in the year 1921 the rate ran about level until the period 1926–30 when there was a pronounced increase which later dropped to the lowest level of the entire period. This increase in this five-year period seemed to be explained as due to greater care in observing and recording mild reactions. Perhaps because of increased attention to mild reactions, the rate of severe reaction fell to a level of only 1.6 per 1000 injections in the years 1929–31 as against 3.1 in the years 1920–22.

From 1925 to 1933, in a comparison of the yearly incidence of postarsphenamine and infectious jaundice Wile and Sams (1934) noted that nearly 60 per cent of their cases of late postarsphenamine jaundice occurred during the years 1930, 1931 and 1932. At the same time about half of the cases of infectious jaundice treated in the hospital from 1923 to 1933 occurred. Stokes, Ruedemann and Lemon (1920) and Ruge (1932) had previously noted a close parallelism between the occurrence of postarsphenamine jaundice and infectious jaundice. In connection with seasons, the incidence of intercurrent infection at various times of the year probably plays a part in the frequency of reactions and in their severity when they occur

Wile and Sams in their study of jaundice in syphilis found that there was a tendency for late jaundice to be slightly more common in the winter months, but this is not so marked as with infectious jaundice. This tendency has been previously noted by others (Todd (1921) Stokes, Ruedemann and Lemon, Ruge) Stokes, Ruedemann and Lemon definitely showed that their cases of jaundice were greatest in number during the months of respiratory and systemic infections, and approximately half the number had associated upper respiratory tract disturbances in the prodromal stage

Nedzel (1946) showed that in winter rabbits succumb to the toxic effects of neoarsphenamine more readily than in the autumn. A smaller number of rabbits survive without severe tissue damage in winter than in autumn. There is a larger number of severely damaged liver and kidneys among the surviving rabbits in winter than in autumn. In winter the livers of rabbits are observed to be relatively more severely damaged than in autumn. For kidneys the reverse relationship holds true. In white rats there were observed a relatively smaller number of severely damaged livers and kidneys in a May and June group as compared with a September and October group. Petersen (1942) has collected evidence indicating the close integration that exists between the meteorologic environment in which the human lives and the condition of the individual as it is reflected in changing susceptibility to drug intoxication.

Nervous States and Reaction to Arsenical Therapy—The influence of nervous factors on any of the arsphenamine reactions is difficult to evaluate Suggestion, apprehension, and undue emphasis on the likelihood of reaction on the part of the treatment room technician or physician at times seem to increase the occurrence of the immediate reaction. Milbradt, Gougerot and

others, including Spiethoff Becker and we ourselves, believe the vagus-sympathetic balance and vascular stability are affected both by arsenicals and emotional tension They are poorly tolerated by vagotonics, patients with toxic goitres and hyperthyroidism and in status lymphaticus.

The mechanism for the production of such effects at least for cutaneous reaction has been discussed by us (1939–40) In addition, the repetition of visits to the clinic or office with the concomitant repetition of the same emotions which the patient experienced at the time of the first visit, when the diagnosis of syphilis was made, may lead to a heightened emotional state on the part of the patient. Eventually prolonged therapy may lead to what Stokes has (1926) called the over treatment syndrome, in which the patient complains of a striking degree of nervous irritability Occasionally according to Cormia patients with this syndrome produced during arsphenamine treatment developed actual arsenical reactions, such as herpes zoster nitritoid crises, and thrombocytopenic purpura.

The following description is quoted from the first edition of this work

Arsphenamine Overtreatment Syndrome.—"There is, however an arsphenamine over treatment syndrome, quite as definite as that observed under mercury though much rarer Instead of becoming depressed, the patient becomes irritable, unstable, and emotional, at times almost hysterical The resultant hyperactivity and the anorexia and gastric disturbance due to nervous tension and hurried eating may lead to loss in weight. A typical case is easily recognized. The patient starts at the least movement or sound; the lips tremble and the eyes become suffused with tears at the slightest sharpness of tone in the examiner In neurosyphilitic patients marked exaggeration of such symptoms as ataxia occurs, not because of cord changes, but because of increased self-consciousness and nervous anxiety A patient once graphically described the mental state to me: "You know how it feels to hold an apple in both hands and twist it so as to break it in half?" he said. "There comes a moment when you can feel as you put the strain on it that the apple is just about to "pop and crack part. Well, I feel like that apple. Bromides, suspension of arsphenamine treatment, and a fishing trip or vacation usually produce a prompt recovery The condition does not appear in patients who have had arsphenamine a year or so before, so that it should not be used as an excuse for under-investigating syphilophobia or patient who comes with the background of latent or asymptomatic neurosyphilis.

Pregnancy and Toxemia of Pregnancy in Treatment Reaction.—The normal effect of pregnancy on the various organs of elimination would lead one to suspect that any other extraneous influence with potential hepatotoxic and nephrotoxic action would increase greatly the likelihood of reaction to the arsenicals in pregnant women. Furthermore the question of whether arsenicals given to pregnant women could possibly increase the likelihood of the so-called toxemia of pregnancy needs fuller investigation.

Several recent discussions of the subject, particularly that of the Cooperative Clinical Group (1936), by McCord (1935) and by Cole (1937) convey the impression that pregnant syphilitic women tolerate arsenical therapy well. McCord has apparently never seen serious treatment reaction or death in the medical supervision of more than 2000 syphilitic pregnant women. On the other hand, Ingraham (1939) in carefully documented study of the complications due to arsenical therapy in syphilitic pregnant women, recorded 7 maternal deaths, the study being based largely on data obtained from antisyphilitic therapy reported from six different sources to the Committee on Maternal Welfare of the Philadelphia County Medical Society since 1931 He was able in addition to collect 35 more deaths from the literature which he believes indicate that the pregnant syphilitic woman is not exempt from any of the severer types of treatment reaction, such as hemorrhagic encephalitis, acute circulatory collapse, damage to liver arsphenamine dermatitis and aplastic anemia, all of which have been causes of death. He believes, moreover that there is evidence to indicate that antisyphilitic treatment may aggravate an already existing toxemia of pregnancy or precipitate an incipient one Moore (1939) has taken exception to Ingraham findings and in study sponsored by Moore and made by Peckham (1911), it was shown that in a series of 13,742 consecutive deliveries at the Johns Hopkins Hospital, the incidence of toxemia of pregnancy was somewhat lower in syphilitic than in non-syphilitic patients. N cor-

relation could be established in the study between the stage of syphilis at the time of its diagnosis and treatment during pregnancy and the frequency of toxemia. Peckham concludes that antisyphilitic treatment administered to syphilitic women during pregnancy does not increase the incidence of toxemia of pregnancy. The question of the influence of pregnancy on treatment reaction is still open, but we feel that conservative individualized therapy during pregnancy with careful attention to detail will yield little or no excess of untoward reaction, in spite of the fact that individual isolated cases of serious reaction may occur in spite of careful control.

In explaining reactivity in pregnancy there seems reason to invoke the influence of nutrition, hygiene, age, nervous state of the patient, and similar collateral factors, too easily overlooked.

Two other considerations involved in pregnancy deserve special mention. Bismuth has been charged with an abortifacient effect of which we have seen no evidence; tryparsamide should not be employed in the pregnant woman because nothing is known of its possible effect on the optic nerves of the child, irrespective of the mother; and malarial therapy should not be invoked during pregnancy, both because of its own serious effect and the abortifacient action of quinine.

Intercurrent Infection and Disease.—One of the enemies of the patient under treatment for syphilis is intercurrent infection, acute, focal, or chronic systemic in type. The large majority of patients carry an unsuspected total load of accessible foci which is added to from time to time by common colds, tonsillitis, infectious diarrheas, grippe, influenza, and bronchitis.

While this subject has been best worked out in connection with cutaneous reaction, undoubtedly the principles can be extended to apply to other types of reaction occurring in patients receiving arsenicals who are subject to intercurrent disease, fungus infection, or foci of infection. The role of intercurrent infection in untoward reactions to antisyphilitic treatment can be divided according to Dudley Smith (1936) into two parts: 1, the harmful effect of antisyphilitic drugs on other infections; and, 2, the part which intercurrent infections play in producing harmful reactions in syphilitic persons. In 1931 Moore and Keidel published an extensive study relative to the appearance of various skin diseases, including exfoliative dermatitis and other less complex reactions such as urticaria, erythema, herpes simplex and so forth following antisyphilitic treatment with arsenicals. They intimated that the secondary dermatoses like herpes could possibly result from something more than the actual local toxic effects of the arsenic, and were inclined to accept Milian's contention (1935) that certain eruptions produced by the arsenicals are like acute exanthemata such as measles, and due to a lighting up of latent bacterial infection. Stokes and Cathcart (1925) were pioneers in calling attention to the influence of focal and intercurrent infections on arsenical dermatitis. In 1934 Stokes and Kulchar extended the concept to include dermatophytosis. According to these authors a part of the influence of infection was probably exerted through the allergic mechanism of arsphenamine sensitization, and involved the conception of multiple balanced and summation effects as suggested by Vaughan (1937) in general, by Harkavy and Hebald (1938) for infectious asthma and arthritis, and by the observations of Moore, Woo and Robinson (1931) on the reactivity of atopics to arsphenamine intradermally. When the infection involves the skin in antecedent or induced dermatitis from other causes, the local dermatitic focus acts as an excitant to the general flare-up following arsenical medication. Dermatophytic infection may apparently act as a participant in a balanced or "summation" allergic complex involving an arsenical, an arsenical extending the range and increasing the severity of the allergic dermatitis response to the drug. A dermatophytic focus may also conceivably serve through the induction of local vasodilatation as the starting point of an "arsenical" dermatitis. Minute amounts of arsphenamine in arsphenamine-sensitive patients may flare up and generalize a local, apparently mycotic, dermatitis. The interaction of a drug on infection allergy may be reversible, and may in some cases take the course of Milian's "activation" of the infectious focus with the appearance of an exanthem of the toxic erythema type and a flare-up of the local focus in the case of bacterial infection, or an exacerbation of a localized mycotic process or a "mycotid" in the case of a fungus infection. Their experience led Stokes and Kulchar to suggest that in dealing with an arsphenamine dermatitis in patients with focal infective lesions, mycotic or bacterial, treatment should be directed, albeit with caution, at the focal as well as at the general process.

In 1937 Stokes and Callaway expressed the opinion that intercurrent infections like influenza may exercise a sensitizing influence to pyogenic and mycotic dermatoses as well as to light. Smith, in his study quotes number of observers, one of whom, Weiss, pointed out in 1925 that fatal accidents following antisyphilitic treatment sometimes can be prevented if caution is observed in treating patients with acute infections, especially pneumonia. The pneumonia induction may be in part due t mechanical and allergic effects involving the pulmonary circulation. He also cited Cormia (1936) in his work on experimental arsphenamine dermatitis which showed that staphylococcus toxin did not increase the incidence or severity of the reactions to arsphenamine in guinea-pigs, and similar results were observed in guinea-pigs infected with streptococci. Smith comment that this does not reproduce the situation found in intercurrent infections in man. Later (1938) Cormia found in contrast with his earlier result that in the presence of low vitamin C diet, chronic focal infection with group C hemolytic streptococcus definitely accentuated the manifestations of cutaneous arsphenamine hypersensitivity This effect was inhibited by high vitamin C int ke hich either reduced arsphenamine reactiveness or increased resistance to the

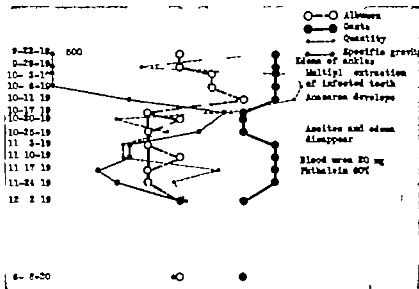


Fig 173.—An illustration of the increased load throw on the kidney by focal infection The patient entered with marked nephrosis, thought t be due to amyloid degeneration. When the focal infection in the teeth was stirred up in the process of extraction he grew markedly orse, albumin increased, and edema and anasarca appeared As he recovered from the xtractions, these signs disappeared and gradual improvement of the renal condition took place, with complete recovery in tw years. His tolerance of treatment as greatly improved and the ultimate therapeutic result as excellent (syphilis of the liver)

streptococcus infection Netter and Urbain (1931) felt, from their studies with the virus of herpes zoster that arsphenamine as well as other agents is responsible for cases of secondary zoster because the drug possibly stirs up to activity latent virus in the ganglia. Much of the jaundice which occurs during arsenical therapy and is attributed t the toxic effects of the drug is in all probability the expression of an epidemic of infectious hepatitis. (Stokes, Ruedemann and Lemon Ruge Wile and Sams; Lane (1939) and others)

The effect of chronic focal infection (dental) in reducing tolerance of treatment is well shown in Fig. 173 in which disturbing a focus of infection decreased treatment tolerance to be followed by improvement on complete removal. The attacks of cystitis and pyelitis associated with infected tabetic bladders are a serious menace though the tolerance of some of these patients for treatment in the intervals between attacks is remarkable and tends to bear out McFarland observation that the kidney while one of the most

abused is probably one of the most tolerant of organs. Fever is a definite contraindication to the administration of the arsphenamines, regardless of cause and particularly so if tuberculosis, respiratory or a chronic pyogenic infection underlies the temperature. Glycosuric diabetics, patients with hyperthyroidism and toxic goiter known cases of lymphatic struma and hemophilia, are very reactive to arsphenamine therapy particularly

Alcohol and Reaction.—The one drug which observation convinces us is dangerous to the patient under treatment for syphilis is alcohol. Its action in favoring cutaneous disturbances such as seborrheic eczema and psoriasis, its stimulating effect on pyogenic infections (furuncle and carbuncle are the terror of the alcoholic as of the diabetic) its vasodilator effect in flushing the skin and promoting vascular instability its possible effects on the liver and its tendency when freely used, to produce a pathologic picture in delirium tremens essentially similar to that produced in hemorrhagic encephalopathy all seem to us unmistakable warnings as to its possible pathogenic rôle in treatment reactions. Its unfavorable effect upon syphilis as a disease is elsewhere discussed.

Disability Due to Syphilis as a Cause of Reaction.—Under this title must be included chiefly the considerations relating to therapeutic shock (Herxheimer effect) and therapeutic paradox discussed on pages 131 and 132 and in connection with syphilis of individual groups of structures in subsequent chapters Where syphilis paves the way through degenerative change for invasion by infection as in the case of the tabetic bladder and the atonic intestinal tract or the duodenal ulcer in the tabetic, it may be conceived as a contributor There is, however no evidence that the syphilitic by virtue of his syphilis *ipso facto* is either more or less tolerant of antisyphilitic drugs than is the normal person.

The Cooperative Clinical Group (1933) found that in early syphilis, the rate for mild reactions was three times higher than for severe reactions. Severe reactions, however showed their highest incidence in primary syphilis followed by lessened incidence in secondary and latent syphilis. Waugh and Milovich (1940) report showed the incidence of severe reactions to be about the same in all the earlier stages of syphilis; being 2.4 per 1000 arsenical injections for primary syphilis, 2.60 for secondary syphilis and 2.41 for latent syphilis. They also found that the incidence was considerably higher for the white patient with primary syphilis and slightly higher for white patients with secondary syphilis. In latent syphilis the incidence for the colored was slightly higher than that for the white patient. Cole and his associates, in their attempt to determine whether the stage of syphilis during which the patient began treatment influenced the type of complication occurring, found that among the early cases the incidence of gastro-intestinal reactions was 27.3 per cent whereas among the latent cases the percentage was nearly doubled—50.6 per cent. A much higher percentage of patients with early syphilis suffered slight skin reactions than of those who began treatment while in the latent stages. There were twice as many nitritoid reactions among the latent cases as among the early cases. Patients with treatment resistant syphilis have been found to be specially reactive to the arsenicals by Jessner (1923–1929) and by Beerman (1936) This fact may be indirectly concerned in the production of treatment resistance since reacting patient can only be given smaller doses which in turn may produce treatment-resistance

One does, however gather the impression, probably more or less traditional that antisyphilitic treatment is better borne by syphilitics than others. In our experience the paretic patient, particularly of the degenerated type, is astonishingly tolerant of huge dosage and protracted treatment which would be borne with difficulty if at all by patients of other types or by normal persons.

System of Treatment as Affecting Reaction.—The Cooperative Clinical Group's investigations in early syphilis have apparently shown that there are significant reaction differences in the aggregate between patients under continuous intermittent, intensive and irregular regimens.

Continuous treatment causes more minor but no more than, if as many major reactions as the definitely less effective intermittent treatment. Jaundice is half as frequent again under intermittent as under continuous treatment, the severe gastro-intestinal disturbances are only slightly more frequent in continuously treated patients; exfoliative dermatitis is approximately as frequent under the one system as under the other; kidney damage is three times as frequent under intermittent as under continuous treatment; and aplastic anemia and purpura about four times as frequent under intermittent as under continuous treatment.

If these figures sustain confirmation in more extended studies they certainly argue that the patient should not be denied the advantages of continuous treatment from the curative standpoint on the theory that he is seriously endangered by grave complications. The minor reactions, including nitritoid crisis, seem to be the only real handicap to the superior continuous system of treatment. The influence of the simultaneous use of a heavy metal with the arsphenamine has already been referred to. It appeared from this study that in any regimen in early syphilis where much heavy metal was given, with or without much arsphenamine, the reactivity was high. It was not greatly increased even by vigorous arsenical treatment (53 *versus* 56 per cent). The minimum of serious reaction is obtained by much arsphenamine and little or no heavy metal, and by much arsphenamine alone. These facts are in accord with the previously mentioned observations on the tendency of reactions to diminish in the longer courses of treatment rather than to increase on the rise of renal tolerance observed by McFarland on stepping-up of elimination discussed *in the previous chapters. They all tend to indicate that the body* acquires a definite tolerance of treatment for syphilis which is an asset in an unknown proportion of cases.

THE GENERAL CLASSIFICATION OF REACTIONS

A certain amount of confusion inevitable on an attempt to retain in memory the enormous range of reaction to treatment for syphilis can be prevented by an attempt at classification. This serves the additional purpose of providing a background for certain general treatment principles which the therapist can have at his finger ends both in knowledge and equipment for dealing with the large majority of cases. Such a schematization is outlined in *Fig 174 and should be carefully inspected. Group I includes therapeutic shock* and therapeutic paradox, fully considered on pages 131 and 132, together with their prevention by means of preparatory treatment (p 220). The effect of structural impairment has been largely considered under general causes of reaction. Group II includes first the general conditions affecting the patient, as previously discussed secondly idiosyncrasy and pseudo-idiosyncrasy and acquired hypersusceptibility *including allergic effects and precocious ter* tiarism.

Idiosyncrasy and Pseudo-Idiosyncrasy as Factors in Reaction.—Idiosyncrasy to antisyphilitic medicaments is an undoubted fact and established beyond question. The statistical and individual study of reaction would tend to indicate that it is particularly important in hemorrhagic disease in some

cases of exfoliative dermatitis occurring on first exhibition of a drug, including arsphenamine, bismuth, mercury and the external application or oral administration of iodide. Individual instances of idiosyncrasy are discussed under the various drugs on pages 213 217 220 257 The aggregate importance of the idiosyncrasy factor cannot be estimated in per cent, but the observer cannot avoid being impressed with the fact that this category of complications seems abnormally frequent among those whose experience with the treatment of syphilis by modern methods is comparatively small. One is led to suspect, therefore, that inexperienced therapeutic management is at least an important factor in the production of what might be called pseudo-idiosyncrasy The patient who is idiosyncratic to all the drugs used in the treatment of syphilis

Fig 174.

A CLINICAL CLASSIFICATION OF REACTIONS

For the Discussion of Prevention and Treatment

1. Reactions contingent on the disease.
    ( ) Therapeutic shock (Herxheimer effect)
    (b) Therapeutic paradox.
    (c) Structural impairment.
2. Reactions contingent on the patient.
    ( ) General conditions.
    (b) Idiosyncrasy and pseudo-idiosyncrasy
    (c) Hypersusceptibility (including allergic effect and precocious tertiarism)
3. Blunders.
    ( ) Acid arsphenamine.
    (b) Toxification of drugs.
    ( ) Water errors
    (d) Tubing reaction.
    (e) Embolism.
    (f) Infection.
4. Technical error
    ( ) Intramuscular injection.
    (b) Intra enous injection.
    ( ) Spinal test.
5. Drug reactions as such.
    ( ) Mouth.
    (b) Gastro-intestinal
    (c) Vascular
    (d) Hematopoietic.
    ( ) Cutaneous.
    (f) Hepatic.
    (g) Renal.
    (h) Pulmonary
    (i) Nervous system.
    (j) Special sense organs.

at one and the same time deserves a very full and careful general medical and at times even a neurological or neuro-psychiatrical examination as well as a dermatological and allergic study to determine the underlying factors and the possibility of their elimination. Among the most common causes of pseudo-idiosyncratic reactivity on the part of patients should be mentioned the following

Causes of Pseudo-idiosyncrasy.—1 Nervous reactivity produced by fear of the disease, noncomprehension of the instructions for the prevention of reaction, underlying neurosis and hysteria, and psychic and physical trauma and pain inflicted in the course of bungling and sometimes even expert treatment.

2 The cutaneous sensitizing effect of technically incorrect intravenous injection of the arsphenamines which allows part of the first dose of the drug to infiltrate the skin. This topic, discussed on page 254 is in reality an aspect of acquired hypersusceptibility

3 Hyperreactivity simulating idiosyncrasy and sensitivity but due in reality to technical errors, first and foremost of which is too rapid or too slow injection of intravenous medicaments. It is impossible to lay too great stress on this factor in the production of pseudo-idiosyncrasy

4 Hyperreactivity simulating idiosyncrasy but due to disregard of an analyzable tolerance factor which is considered in the next section under general principles of reaction prevention.

Where, in spite of attention to all the details involved in the above items, the patient is still persistently reactive, the practitioner would be well advised to secure expert advice before abandoning treatment or increasing his difficulties by haphazard trials of various possibilities. Shift of drug and various substitutions are considered on page 389

Hypersusceptibility and Allergic Effects in Reactions.—These are presented in detail on page 253

Induction of Precocious Tertiarism by Inadequate Treatment.—Precocious tertiarism and violent allergic response to a syphilitic infection following a few injections of a trivalent arsenical is a phenomenon of an entirely different order from trivalent arsenical cutaneous sensitivity and probably involves the reaction of the tissues to the disease-producing agent rather than to the drug used in treatment. The frequency of induced malignant syphilis or precocious tertiarism as the result of two or three injections of a trivalent arsenical followed by a rest period or lapse, is not precisely known but the dangerous and destructive reactivity thus induced by inadequate treatment is a serious complication In the chapter on relapse illustrations of the huge ulcerative lesions, the intractable gummatous manifestations, rupial eruptions and so forth, which may follow the suspension of treatment in a patient who has received only a small amount of trivalent arsenical without heavy metal protection, are well illustrated (Figs 423 434) The remedy is an obvious one —under no circumstances should a patient particularly with early syphilis be given an arsenical without an accompanying or ensuing heavy metal and inasmuch as most instances of precocious tertiarism occur in patients who have lapsed treatment before it was thought advisable to introduce the heavy metal therapy this fact seems a justifiable argument in favor of simultaneous use of the two types of drug rather than their alternate use. Malignant syphilis and precocious tertiarism should largely disappear when the axiom "No short courses and no arsenical without heavy metal" is universally accepted.

THE GENERAL PRINCIPLES OF REACTION PREVENTION

The foregoing section has dealt largely with the inevitable. The ensuing section will deal with those forms of reaction which result from blunders, technical errors and drug reactions as such, and which are therefore largely avoidable and to a high degree treatable. Before considering them individually the general principles of reaction prevention and treatment may be reviewed

General Appraisal and Restorative Measures.—As in the determination of the aims and possibilities of treatment, so in the prevention of complications the first essential to a reactionless course is a thoroughgoing physical ex

amination with a consideration of the general factors influencing tolerance and reactivity as discussed in the preceding section.

With distressing frequency the single-track mindedness, so to speak, which one of us (J. H. S.) has labeled with the term "Wassermannism" or "serologism" (see Fig. 150) leads to the initiation of treatment without even a preliminary effort to survey the situation with reference to tolerance. The sight of a positive serologic report is to the uncritical doctor like the sighting of the "Jolly Roger" in piratical days, a signal for opening fire without parley irrespective of whether the opponent is yawl, sloop or frigate. If the patient be sound in wind and limb, he will probably tolerate all that may be needed to control or cure his infection. If on the other hand, he present remediable defects, they should be identified and corrected.

It is desirable at the outset if possible to initiate a physical overhauling which restores the infected person to the general level of normality for his time of life. The removal or treatment of focal infections, early rather than late, general hygiene, mouth prophylaxis, attention to diet, alcohol, and constipation, each becomes individually important. The essentials of this mouth prophylaxis are given in Fig. 175, the measures aiming in general at

Fig. 175.

ORAL HYGIENE FOR THE SYPHILITIC PATIENT

1. Carious teeth out or filled.
2. Gum pockets cleaned and treated, teeth scaled.
3. An alkaline potassium chlorate toothpaste used twice daily with a medium brush.
4. Wash mouth after eating with zinc chloride mouth wash (½ of 1 per cent in Liq. antisepticus alkalinus).
5. Clean dentures as well as teeth.
6. Then paint gums inside and out with a mixture of 1 part tincture kino, 2 parts tincture of myrrh.
7. If signs of salivation or gingivitis appear, change to half strength hydrogen peroxide solution.
8. Have buried teeth out at the start.
9. Have gum flaps over third molar teeth removed.
10. Watch devitalized teeth closely. If possible remove them, substituting adequate removable and cleanable dentures.
11. Avoid devitalizing teeth during treatment.
12. With mercurials avoid acid or sour foods.
13. For the best mouth hygiene, avoid sugar and sweets.
14. Remember bismuth pigment betrays the patient to family or dentist.
15. Dental help is desirable but much can be done *without it*.
16. Dental hygiene should precede tonsillectomy.

the discouragement of saprophytic flora and the prevention of the formation of hydrogen sulphide in the mouth.

Dietary Management.—This should be appropriate to the situation, and is summarized in Figures 178 and 179.

Instructions to the patient for the management of the gastro-intestinal phase of his reactions in so far as he can take care of it himself are given in Fig. 176.

Preparation and After-care—Vigilance.—The cardinal ingredient of all plans to prevent reaction is unremitting alertness and vigilance. It is impossible to overemphasize this element in the prevention of trouble for it constantly suffers obscurity and lapse even in the best regulated practices and clinics. The initial energy required to bring the safety factor in treatment

to the highest possible level is very high and a service directed by an apathetic, overworked or fatigued chief and personnel may be counted upon to yield a considerable crop of reactions, unfortunately many of them serious. Even in a relatively leisurely office practice it is difficult and even annoying for physician and patient to go time after time through the seeming rigmarole which

Fig 170

A GASTRO-INTESTINAL REGIMEN FOR THE PATIENT UNDER TREATMENT

1 Encourage regularity in eating, slow chewing
2 Relieve anxiety for its depressant effect on the tract in some, its induction of spasm in others.
3 Meet constipation by considering the type, put high-strung nervous patients with spasm on bland diet, atonic types on roughage and increased fluids with exercise and massage
4 The tendency of treatment is to produce diarrhea not constipation. Therefore avoid roughage in general.
5 Avoid catharsis, except mildly after arsphenamine.
6 Do not give cascara as a cathartic. Use mild saline, castor oil, or phenolphthalein.
7 A mild laxative is better than an uncontrolled constipation under treatment, but a curative regime is even better
8. If enemas are used, employ physiologic saline, or water
9 Permit meat, eggs, fish, the softer vegetables (avoid fruits with small seeds, use tomato pulp and juice, excluding seeds) baked potato three times weekly graham bread, cooked whole-grain cereals. Limit desserts to custards, junkets, gelatin, with little sugar pulpy and seedless fruits, unsweetened. The coarser vegetables (spinach, celery radishes, onions, turnips, cabbage) must be cooked and put through a strainer or very finely comminuted
10 Emphasize fats by insisting on ( ) whole milk reinforced by cream, ½ to 1 pint to the quart (b) butter and salt or cream on cereals (no sugar); ( ) butter on vegetables; (d) cream, whipped, on desserts; ( ) mayonnaise and oil dressings; (f) peanut butter (g) nuts (h) cream with effervescent mineral waters in underweight patients (8 oz., equal parts, between meals) Avoid during intensive arsenical therapy
11 Sharply restrict or exclude ( ) sugar as candy honey syrups, soda-fountain and effervescent or syrupy drinks, ice-cream, pastries (b) the starchy puddings (rice, cornstarch bread pudding, dumplings); ( ) high proportions of macaroni rice corn meal (d) bran as such.
12. The Vitamin groups A and B may be increased by cod liver and halibut liver oil and by wheat germ or brewers' yeast respectively and the B group should be added to high fat diets (ketogenic type) Vitamin C may be given in tablet form or as solvent for the arsenical
13. Edentulous patients must have dentures or use the meat grinder
14. Administer alkalis only for definite reason, avoiding the soda and magnesia habits.
15 Do not give hydrochloric acid by mouth to patient on heavy metal (risk of salivation) without special precaution (alkaline rinses, etc)
16. Avoid sour foods in mercurial therapy (see Oral Hygiene)
17 No more than light wine for carminative effect with meals, and not that except for medical reasons. No *cocktails, highballs, "hard" liquors.*

if conscientiously carried out, is the essential ritual of protection In the effort to systematize these elements in our own practice and clinic we have tried to emphasize four items

(1) The proper questioning of the patient as to his response to the previous treatment (2) a minimal medical inspection (3) weekly observation with the occasional performance of indicated special tests, including urine differential blood count and icterus index and (4) systematic instruction of the patient in a technic of preparation and after-care Particularly when treatment is to

be conducted as an ambulatory procedure, the conscientious carrying out of detail under these four heads will be found a great aid in the general prevention of reaction.

The Questionnaire.—In 1931 one of us (J H S.) drew up a question form mounted on a card under celluloid which was presented to each literate and reasonably intelligent patient to be read and answered by him before each treatment. This question form is shown in Fig 177 A card or chart bearing it may

Fig 177

PREPARATION OF PATIENT FOR TREATMENT—QUESTION FORM

Questions To Be Answered Before Receiving Treatment:

Each time the nurse prepares you for treatment, she will hand you this card. Please read the questions one at a time out loud and answer each one in her presence. Think carefully and give correct answers. In this way you can do a great deal to protect you from disturbance or reaction caused by the medicines you are receiving.

1. *How do you feel?*
2. Were you sick at your stomach, or were your bowels loose after the last injection.
3. Any trouble with arm or hip?
4. Is your mouth sore?
5. Any pain down the legs?
6. Did you itch?
7. Did your skin get red or break out?
8. Is it red, itchy or broken out anywhere now?
9. Are you getting up nights to pass water?
10. Is your urine dark or reddish in color?
11. Did you bleed from the gums?
12. Were your bowel movements black
13. Were your bowel movements white or clay-colored?
14. Were or are there any spots on your skin since last treatment, especially black and blue ones?
15. Are you having a cold? Is it in your head or chest?
16. Is the trouble for which you came to us getting better or worse, or is there no change?

be mounted or painted on the waiting room or treatment wall. Where the patient cannot be relied upon to read it intelligently the questions should be asked, if necessary with the aid of an interpreter or by sign language to secure the required information. The responses to these questions cover practically all of the warning signs of a developing intolerance of over-dosage and too-rapid injection of incorrect intramuscular intravenous entry and injection of impending jaundice, dermatitis and purpura of the onset of an acute respiratory infection and of the progress of the patient. It is impossible to overemphasize the extreme importance of the questions relating to itching rashes, and signs of hemorrhage. Time and again patients admitted to wards of hospitals in serious condition and conscientious physicians attending them have given unmistakable accounts of symptoms which were either not fully inquired into or slurred over at the injection next preceding the one which resulted in a perhaps fatal exfoliative dermatitis or hemorrhagic complication. In our own experience and observation this has happened *a number of times even in* services and practice which we supposed we had under complete control. Such experiences illustrate less the inevitability of grave consequences from a lapse in vigilance than they do the paramount necessity for maintaining standards of practice fully comparable to those of the best surgical and other critical forms of medical work.

Emphasis should here be placed again upon the significance of nitritoid

reactions (see p. 244) and gastro-intestinal intolerance as warnings of a developing inability to carry treatment unless compensated by detoxifying measures. Not alone for the subjective relief and improved cooperation of the patient, but because it is positively dangerous to permit steadily increasing increments of reaction to grow unchecked, the appearance even of the minor types of reaction in a patient should be closely watched and scrutinized for every possible cause Vigilance does not, however protect against the idiosyncratic factors involved in hemorrhagic encephalopathy exfoliative dermatitis and fulminating acute arsenical poisoning with atrophy of the liver

Minimal Medical Inspection.—Many patients are not sufficiently observing nor do they present evidence visible to them, of impending complications. Accordingly a minimal medical inspection is indispensable to a smoothly conducted practice. The recommendation that a patient be stripped and completely examined before each treatment is ideal but impracticable. A reason

Fig 178.

PREPARATION OF PATIENT FOR TREATMENT—
MINIMAL MEDICAL INSPECTION

Fix your eyes on the patient face, the bared neck (and shoulder if possible) the bends of the elbow and the wrists and look in the mouth. Have him drop his sock or stocking.

Before treatment is given be sure you have inspected

1 **Condition of the Available Veins.**—Palpation is quite as important as inspection, for *thrombosed vein can sometimes be recognized as such only by the way it jumps* under the palpating finger and resist compression.

2. **Condition of the Buttock.**—Deep induration should be sought for together with any trace of erythema, superficial nodules, tenderness over the sciatic nerve, uncomplicated deep tenderness.

3 **Pink stippling or signs of irritability (rash) of the skin about the neck, the face the elbow flexures.** The latter especially will be seen on baring the arm for intravenous injection and may pass unnoticed by the patient.

4 **Color of the Sclerae.**—The patient should be viewed in good daylight, if possible

5 **Petechiæ** on the gums, ankles and wrists.

6. **Fetid odor of the breath.** This suggests bismuth overdosage.

7 **Involution or progression of visible lesions of the disease** especially chancre and secondaries.

MANY COMPLICATIONS GIVE DEFINITE WARNING LOOK FOR THEM
AN OVERSIGHT MAY BE FATAL

able compromise with this requirement is presented in Fig. 178 In highly organized clinics such as that of Colonel Harrison at St. Thomas s Hospital, London, the medical officer charged with the duty of passing the patient for treatment occupied a definite station with a strong daylight illumination or daylight corrected electric light playing upon the patient. The objection of private patients to divesting themselves of enough of their upper garments to expose neck, arms, and shoulders must be overruled Dermatitis most frequently appears at the flexures and on the face below the eyes and sides of the neck· purpura on the mucosae and about the wrists and ankles. The beginnings of the nitritoid reaction during treatment cannot be detected satisfactorily without this degree of exposure at the time the injection is given If the physician will retain the items on which he desires information in mind during the process of the treatment interview he will find it possible without embarrassment to cover each and every point. His principal problem will be to remember and

to take the time. Finally only by observing the state of the active lesion for which the patient is being treated can one judge of the efficacy of much of the treatment and the effectiveness of the drugs. It is particularly desirable to

Fig 179

DIRECTIONS TO THE PATIENT TO BE FOLLOWED BEFORE AND AFTER TREATMENT

Before the "Arm" Treatment:
1. Bowels should move the morning of the treatment day. Take mild laxative the night before if in doubt or ask for directions if habitually constipated.
2. Plan to eat very lightly the meal before treatment and the meal after: tea and toast, cereal, no meat, no rich foods, nor coarse vegetables.
3. Eat nothing within two hours before treatment.
4. Report cold, cough, sore throat, loose bowels, fever before you come for treatment.
5. Watch your skin, bowels, urine, and report anything wrong before treatment, whether questioned or not.

After the "Arm" Treatment
1. Go home and lie down if possible. If not, try to avoid physical work and moving about. If feeling out of sorts, go to bed.
2. Eat lightly the meal after treatment. Under no circumstances eat meat, coarse vegetables, sea food, or pastry.
3. On the following day resume full diet.
4. While taking treatment eat freely of meat, eggs, butter and cream. Avoid starches and sweets.
5. Use no alcohol.
6. Do not be unnecessarily alarmed over headache or stomach upset after treatment. Take chipped ice, chewing the ice and swallowing it without letting it melt in the mouth. If decidedly nauseated, swallow a glass of water containing level teaspoonful of baking soda, and vomit if necessary. Use ice-bag on the pit of the stomach if possible. Report by telephone if not relieved. For headache, use cold compress or ice-bag.
7. If more than four liquid bowel movements, follow treatment within six hours, accompanied by cramps, take teaspoonful of paregoric every half hour for 3 doses; eat only hot milk toast and stay in bed. Report if not relieved.
8. If the bowels have moved less than three times before the morning after treatment, take cathartic before breakfast; either one-half bottle of citrate of magnesia, or glass of Pluto water or tablespoonful of Epsom salts or an ounce of castor oil with orange and lemon juice and a pinch of baking soda. If your bowels do not then move by afternoon, telephone for advice.
9. If the skin itches or breaks out after treatment, or becomes yellow or spotted, or the gums bleed, or the urine gets brown or red, telephone for advice.
10. Bring in urine specimen, 6 ounces, one half collected on going to bed, the other half on rising in the morning. Mix the two and put your name and the date on the clean filled bottle.

After "Hip" Treatment
1. The first three or four treatments may cause discomfort, but the tissue soon becomes accustomed.
2. There is usually some stiffness for two to four hours, or the day after treatment.
3. Use the muscles by walking, golf or other exercise to promote absorption.
4. Massage the hip over the injection deeply and firmly with the flat of the hand, especially just after treatment.
5. At bedtime, on three to five nights a week, fill the bathtub 6 inches deep with hot water. Sit in it, leaning back enough to keep the buttocks covered, and resting the feet on the end or sides of the tub, gently massage each buttock under the water, keeping it hot, and remaining in the sitz bath twenty minutes. This is preferable to hot compresses or the hot-water bag or electric pad.
6. Report any serious discomfort before the next treatment.

watch the involution of primary and secondary lesions when neoarsphenamine is being employed, for without darkfield control this is almost the only available means of detecting ineffective lots and drug resistance.

Weekly Observation.—Losing sight of the patient in hurry and routine leads particularly to accidents, and the ritual of inspection should be repeated even in patients on relatively mild medication at intervals appropriate to the drug and state of the case. The temptation, particularly under uneventful bismuth therapy is to have the technician carry through procedures week after week without more than casual inquiry Patients themselves become lax in the matter of bringing urine specimens, and insistence, amounting almost to discipline, is sometimes necessary Patients on heavy-metal therapy need questioning in regard to their local reactions, their gastro-intestinal tracts and mouths and evidence of polyuria and renal irritation particularly These items are covered in the general questionnaire which can be abbreviated to this extent in dealing with patients not receiving the arsenicals.

Instruction of the Patient in Preparation and After-care.—In ambulatory treatment especially the patient often becomes a more important factor in the prevention of reactions than the physician himself. For this reason it is essential to make every effort to interest and inform him without rendering him introspective or frightened. The direction sheet given in Fig. 179 outlines the essential requirements in a form to give to patients for their own guidance In a large treatment service it may be necessary to have a medical officer on call to meet the inquiries of patients, but the more closely the patient can follow these directions, the less the likelihood that he will need to summon aid Individual points will require emphasis and reemphasis and the reactions incident to a service, particularly in the minor field, will rise with the obtuseness of its clientele of course, but even more with the failure of the physician to put energy attention to detail and persuasive power with patients into his work.

Functional Tests—the Weekly Urine.—This was an essential feature of treatment in mercurial days under the bismuth regimen, weekly examinations are unnecessary but once in two weeks is a minimum of precaution with present knowledge. The items to be considered include evidence of renal irritation seriatim in the form of polyuria (low specific gravity) albumin casts, usually hyaline or granular and red blood cells. Abelin or Dickinson tests may be performed on urines by special students of the questions involved but are not recommended as routine, even in large clinics (Lloyd and Lloyd) All urines should be tested for bile, though it can usually be detected in the sclerae almost as soon as it is obvious in the urine. While pus is not an accompaniment of arsenical or heavy metal nephrosis, as a rule, its presence is important especially in tabetic neurosyphilis as evidence of the state of the kidney and bladder damaged by retention and infection. The phenolsulphonphthalein test for renal function should be performed at the outset in tabetics for the estimation of renal tolerance and general condition, but is unnecessary in the protection of the kidney during routine treatment.

Blood urea nitrogen should be obtained on tabetic patients before treatment is instituted, but is unnecessary as a routine except in patients under malarial therapy in whom a rise in blood urea nitrogen while under treatment is a danger sign.

Liver functional tests except as a preliminary to intensive methods such as intravenous drip are of debatable utility We do not believe it is necessary to obtain the icterus index after each arsphenamine injection as has sometimes been advocated, but it would seem advisable if the service has the facilities available or the private patient can afford it to secure this test once in six or

eight weeks during the longer courses of arsphenamine treatment which are growing in popularity or at any time that stormy course or puzzling symptoms appear

The development of a test for detecting cutaneous susceptibility in time to have preventive value would be a decided advance At the present time no such tests exist, the patch and intracutaneous sensitization tests described on p 255 being of known value only in detecting cutaneous sensitiveness after rather than before the explosion. On the other hand, these tests reach a considerable degree of value when employed for the differentiation of the so-called "ninth-day erythema" from the onset of exfoliative dermatitis and in deciding the fitness of a patient seen in consultation after a ninth-day erythema has developed for the continuance of arsenical treatment. The technic is discussed on p. 285

Periodic differential counts of the white blood cells with emphasis particularly on the appearance of an abnormal proportion of eosinophils and of nucleated reds are probably advisable in patients showing significant intolerance of treatment or in those receiving long courses. The indications must be determined by the individual case. Moore and Foley emphasize the value of such differential counts in warning of the seriousness of itching and slight rashes and of stomatitis as threats of impending exfoliative dermatitis or aplastic anemia. Schwind (1945) found in fourteen patients receiving five-day intensive drip arsenotherapy that there were no significant changes in the bone marrow of the patients in the absence of specific idiosyncrasy evidenced to arsenical drugs.

Special Tests in Pregnancy—Before an intravenous injection is given to a pregnant woman and on each occasion a blood pressure reading should be taken and the urine passed on the morning of the treatment day should be tested for albumin, at least. This can be performed as part of the minimal medical inspection and is the only means of detecting the threat of eclampsia and intoxications of pregnancy in time to prevent the precipitation of critical accidents by treatment. The patient should not, however be alarmed by the procedure.

Special Tests in Intensive Intravenous Arsenotherapy—Leifer (1940) states that the routine examinations for the control of reaction include (1) daily urinalyses with determination of urobilin (2) determination of the urea nitrogen content of the blood and the icterus index at the beginning and at the termination of treatment, (3) complete blood count, including that of the platelets, at the beginning and at the termination of treatment, (4) darkfield examination of material from all open lesions (5) estimations of renal function by determination of the specific gravity of the urine (6) special tests of hepatic function by the bilirubin method.

GENERAL PRINCIPLES OF TREATMENT OF REACTIONS

The general character of the reaction mechanism in the administration of arsenic and heavy metals makes possible a certain degree of generalization on methods of treatment.

Emergency Aid.—A number of treatment reactions, but fortunately not often the most serious ones, are matters of emergency often to be dealt with in the treatment room, with the patient on the table. In such situations, equipment on the spot, experience, team-work, discipline and speed may save discomfort and even life itself Figure 180 summarizes the equipment of the emergency cart or tray

Detoxification.—The first group of treatment procedures of general availability may be spoken of as "detoxifying measures. These are directed at enabling the body tissues and in some cases particularly the excretory organs to carry the injury inflicted by the poisonous element in the treatment without

sons, even though its evaluation is not complete, it should be routinely used wherever it seems probable that one or other of the drugs mentioned is responsible for reaction or complications.

Calcium.—The wave of popularity which has brought calcium into such therapeutic prominence in general medicine has led to interesting and probably important applications in the control of reaction to antisyphilitic treatment.

Spiethoff and Wiesenack in 1920 employed Afenil" and 10 per cent calcium chloride solution as preliminary treatment in intravenous injection of the arsphenamines and likewise used calcium-containing solvents for the drug Their favorable results in the reduction of toxicity were later confirmed by Stümpke, Jacobsohn, and Sklarz, by Schumacher and most recently by Gerwig Schumacher explains the effect as due to a reduction in the length of time that soluble arsphenamine circulates in the blood stream and an increase in spirillicidal effect. Gerwig, in group of 24 cases, showed that angioneurotic symptoms following injection, rise of temperature, malaise and gastro-intestinal disturbances were particularly favorably influenced by the employment of 10 per cent solution of calcium gluconate, the neoarsphenamine being dissolved in the contents of 10 cc. ampule

The mechanism of action of calcium thus employed is probably complex and not fully understood. At least a part of the effect follows the lines suggested by Frei, Nathan, and Munk, Krowarz, Luithlen, Chiari and Januschke, and Klauder and Brown in influencing the background of anaphylactic reaction, the vasomotor phenomena of arsenical complications and the calcium-potassium balance of the skin in which calcium plays the role of sedative. Jui-Wu Mu (1933) opposes this view Lewin (1927) had suggested increased rather than decreased toxic effects from the use of calcium chloride solution as a solvent.

Our experience accords with that summarized favorably above. In two cases in which suspension of treatment was threatened by pronounced gastro-intestinal reaction, treatment was continued without serious difficulty following the simultaneous administration of 10 per cent calcium gluconate solution with the intravenously injected neoarsphenamine and arsphenamine (606) The pruritic symptoms without dermatitis observed in some patients have also responded very well. In the treatment of the late residues of arsphenamine dermatitis in which the acute phase has passed but an annoying vasomotor instability with scattered outbreaks of dermatitis persists, calcium is very useful in conjunction with ultraviolet light and roentgen-ray The administration of the drug in large doses by mouth (60 to 75 grains of the effervescent lactate or the gluconate twice daily in addition to the intramuscular injection of the 10 per cent solution in 5 to 10 cc. doses) is desirable. The intramuscular injections may be given from one to three times weekly If the drug is given intravenously the rate of injection should be extremely slow to avoid the disagreeable flushing and the possibility of capillary emboli.

Glucose —Glucose as a 40 per cent aqueous solution may be employed both as a buffer and for possible therapeutic and prophylactic effects on the body tissues. Harrison endorses Dreyfus's use of it as a solvent for neoarsphenamine with the provision that the solution be made alkaline by the addition of 4 cc. of 4 per cent NaOH per 250 cc of glucose solution to raise the pH A part of the effect may of course, be due to the alkali but Harrison noted marked reduction in minor reactions in his clinic with the use of this solvent. Harrison stated that in certain German clinics arsphenamine erythemas were treated at the outset by injections of 20 to 30 cc. of 20 per cent dextrose intravenously coincidently with 10 to 20 units of insulin to fix it in

the liver. Loren Shaffer (1934) reported good results in the treatment of post arsphenamine exfoliative dermatitis with glucose intravenously. The course of his cases was materially shortened by this means. The effect of carbohydrate in influencing the liver in arsenical intoxication must be further studied, in view of Craven's and other observations on the bad effects of a high carbohydrate diet. The unfavorable action observed by these workers may be due not so much to the absorbed carbohydrate as to the effect of such diets on toxin production by micro-organisms in the intestinal tract. Glucose in arsenical dermatitis may be used in doses of 20 cc. of the 50 per cent solution once or twice a day.

Venesection.—This half-forgotten method of dealing with acute intoxications deserves reconsideration. Harrison mentions it (withdrawal of 500 cc. of blood from cubital vein) in convulsive reactions following arsphenamine, and it should be tried in conjunction with the administration of Fischer's solution in acid arsphenamine accidents and supposed eclamptic seizures.

Influence of Detoxification on Therapeutic Effect.—It is very proper to raise the question as to whether the use of detoxifying agents as prophylaxis either in solutions for making up the arsphenamines or when separately administered, has an effect in reducing the therapeutic action of the drug. While in the main, the existing evidence is against any such action the question is unsettled. Voegtlin and Dyer, Citron and others showed that the spirillicidal action of the arsphenamines is unimpaired by sodium thiosulphate. Calcium and glucose have no impairing effect. Vitamin C has no deterrent effect on therapeutic action.

Other Detoxification Methods.—Mention has already been made of vitamin C and its derivatives for detoxification of the arsenicals (diet, etc.). Innumerable other substances have been proposed for the same purpose (Doak 1941). Among the more important are: degradation products of protein (amino-acids) (Rebaudi, 1934; Bensch, 1933); and sodium dehydrocholate (decholin) (Jacchia and Truffi, 1934; Shaw, 1930; Appel and Jankelson, 1936; Kolmer, 1940).

Protection of the Liver Cell.—The influence of diet has been discussed and it may again well be emphasized that the clinical good effects of the use of glucose intravenously are not necessarily to be confused with the unfavorable effects of a high carbohydrate diet. The belief that hepatic injury plays an important part in other types of arsphenamine reaction than jaundice and acute yellow atrophy and can be prevented or compensated by administering liver extract has been experimentally studied by Milbradt and applied clinically by Spiethoff. By blocking the reticuloendothelial system of the rabbit, which threw the entire load of the subsequently administered arsphenamine on the liver, Milbradt showed that the administration of liver extract protected the treated animal against the severe intoxication which ensued in the untreated. He experimentally related this form of protection to the prevention of dermatitis by sensitizing white rats to neoarsphenamine and protecting certain of them against cutaneous sensitization eruptive manifestations by liver extract (Hepatrat). Spiethoff reported excellent results in arsphenamine and heavy metal poisonings, including exfoliative dermatitis in the course of treatment, from the subcutaneous or intramuscular use of this liver preparation and regards its use as a form of substitution therapy, though the response obtained in psoriasis suggests a nonspecific protein phase. MacKee and Astrachan (1940) found liver extract (Parke Davis and Company) useful in various manifestations of arsenical intolerance, using a dosage of 2 cc. intramuscularly given either just prior to the arsenical injection or in courses of 12 injections at the rate of three per week, in cases of established intolerance.

Change of Drug.—It has been shown that reacting patients tend to react more than once. In some patients this tendency is so pronounced that it is impossible to overcome it by the ordinary preventive and treatment pro-

cedures appropriate to the particular type of reaction. In such cases modification of the treatment regimen by a change of drug becomes the only method of dealing with the situation. Nitritoid gastro-intestinal and cutaneous reactions particularly fall into this category A shift from arsphenamine to neoarsphenamine or from neoarsphenamine to bismuth arsphenamine sulphonate a shift from arsphenamine (606) alone to half doses of neoarsphenamine and bismuth administered simultaneously a shift from an arsphenamine to bismuth alone as a result of inescapable intolerance or a shift from any of these preparations to mapharsen are typical examples of the devices that must be used In latent and late syphilis the consequences of such a shift are easier of adjustment than in early syphilis, where depriving the patient of the benefit of an arsphenamine may lead to serious consequences in relapse neurorecurrence or during pregnancy in the infection of the child Before a shift is made detoxification by the various general methods should have been attempted and only when this fails should a method of less intrinsic effectiveness be adopted.

Preparation and After-care.—Considerations involving the preparation and after-care of patients for arsenical and heavy metal therapy (not including tryparsamide which is separately considered on p 1042) are outlined from the standpoint of instructions to the patient in Fig 179

Fever —The patient s temperature should invariably be taken as a preliminary to any form of intravenous therapy As a complication of treatment for syphilis fever may be a manifestation of therapeutic shock (Herxheimer effect) or occur as part of cutaneous and other reactions. As a solitary symptom it may occur occasionally as a slight afternoon rise of temperature in the course of mercurial treatment, possibly due to lighting up of a focus of infection "ninth day erythema" or to the syndrome of bismuth grippe, conditions usually accompanied by arthralgia and malaise with some gastro-intestinal disturbance. After arsenical administration fever is usually accompanied by other symptoms but it may be the only reaction to an arsenical given intramuscularly in patients in whom there is no reason to suspect either a Herxheimer effect or a local abscess. It may be a symptom of embolism in some silent structure such as the central portion of the lung or the spleen. In intensive arsenotherapy fever especially when associated with an eruption, is an extremely common reaction symptom ("secondary fever" 64 per cent with neoarsphenamine 12 per cent with mapharsen in the five-day drip arsenotherapy) It also occurs as an important evidence of intolerance in eighteen and twelve week mapharsen systems. As a rule, however the occurrence of fever as a definite and protracted reaction in treatment for syphilis should stimulate an immediate search for an intercurrent infection, especially a tuberculous focus which may have been present and unrecognized before treatment began or which may have been stirred up by the treatment. Malaria should be looked for in Southern patients.

The importance of the taking of patient temperature before giving an arsphenamine treatment, in order to be fair to the drug as well as the patient, is well illustrated by the case of seemingly healthy child ith tuberculid bom one of us (J H S.) as asked to treat with arsphenamine for nonspecific effects. The child entered the hospital, rosy-cheeked specimen of healthy girlhood, and was ready to be taken t the treatment room when it was found that her temperature as 101 F Treatment as not given, and some four months later she died of miliary tuberculosis. If she had received the injection of arsphenamine the drug would, of course, have been held responsible for lighting-up of the tuberculous focus and the fatal issue. Fever in syphilis is, in our experience, one of the first symptoms t disappear under arsphenamine treatment.

Water errors may be the cause of chill with fever as a treatment reaction and usually affect a considerable number of patients in a group This reaction may follow sodium iodide administration intravenously when either drug or solvent is impure. The tubing reaction (see p 392) is another source of sharp febrile reactions in groups of patients under treatment.

On one occasion on the Mayo Clinic service it was noticed by the operators that showers of reactions occurred on Mondays. Part of it was undoubtedly due to haste in injecting but the reactions did not finally disappear until after it was discovered that water that was distilled on Friday and Saturday was being kept over by an inexperienced attendant and supplied to the operating rooms on Monday morning without redistillation.

In the matter of pretreatment preparation of the gastro-intestinal tract, wide differences of opinion have existed Particularly where "606" is used and on services operating under pressure with an expected high incidence of reactions, *an outright preoperative preparation* with a cathartic and a fasting stomach throughout the treatment day was advocated by British base hospitals during World War I Lees, on the other hand disapproves. A very light meal (tea and buttered toast) before and a moderate food intake after treatment has seemed to us satisfactory O'Donovan has insisted that no one should undertake the treatment of syphilis without having immediately available, facilities for the hospitalization of the reacting patient, and this we believe is in general true. When emergencies occur the delay in serious cases may be sufficient, as in acid arsphenamine administration, to cause loss of life. The average requirements for emergency use in the after-care of reacting patients are outlined in Fig 180

THE SPECIAL REACTIONS AND COMPLICATIONS. DESCRIPTION AND TREATMENT

We return now to the general clinical classification of reactions (Fig 174) for the special application of general treatment principles and additional special methods.

Blunders (1)—Acid Arsphenamine.—The most terrifying and often the most unpardonable of blunders in the use of the arsphenamines is the administration of concentrated unneutralized arsphenamine (606) in place of neoarsphenamine.

Not a year passes that this accident does not occur often in a well-managed clinic or hospital rather than in the office of the inexperienced practitioner One of us (J H. S.) has, on one occasion, been caught by a nurse on the verge of doing this very thing The consequences stand out like a lighthouse not only to operator and staff but to the newspaper-reading public, which thereupon promptly damns the modern treatment of syphilis without further thought or discussion. The prevention of this accident on syphilological services can be accomplished only by the most unceasing vigilance, and no chief ever feels himself entirely free of the anxiety which some of his less experienced associates and assistants may suddenly and without warning convert into an agonizing reality Much can be accomplished by training every hospital intern to read labels systematically in advance of the preparation of any drug by insisting that no package of arsphenamine (usually plainly marked) shall be opened or prepared for opening except in the presence of the operator that the label shall be kept attached from start to finish and no preparation ever made up from an unlabeled ampule that the business of mixing arsphenamine, like that of steering a ship, should be governed by the rule "Don't talk to the man at the wheel" and by the thorough drilling-in of the rule that any arsphenamine preparation which does not completely and almost immediately dissolve in 10 cc of water is to be thrown out. The label can be kept attached by a rubber band, even with heat sterilization of the ampule and the solubility of "606" in the vast majority of preparations is such that there is at least a very definite retardation if not

an absolute refusal to go into complete solution in this amount of water This fact should at once arouse suspicion. Only experts can be relied upon to distinguish the two drugs by their color and odor To prevent the *administration of diluted but unneutralized arsphenamine, which* fortunately is less dangerous than the administration of concentrated arsphenamine solution, a drop or two of phenolphthalein (alcoholic) solution added to every bulk solution of an arsphenamine to turn pink on alkalinization, is a very useful protection devised by Chambers.

The symptoms of acid arsphenamine administration depend on the concentration of the solution. With concentrated arsphenamine administered at the rate too often customary for neoarsphenamine, almost nothing may happen for the first few seconds to a few minutes. The patient may even rise from the table, don his clothing, and proceed to the corridor or the street before death overtakes him. A complaint of agonizing pain in the arm and in the small of the back, choking sensation, collapse or syncope and death before any assistance can be rendered is the usual rule. When the dilute solution has been given at a slow rate, symptoms usually begin to appear before the first decigram is administered. The complaints are identical with those in the case of the concentrated solution and the general effect essentially the same but fortunately more retarded and less often fatal. Suspicion should always be instantly aroused by any complaint on the part of the patient of pain in the back during an injection, and of pallor or the appearance of collapse instead of the scarlet flush of a beginning nitritoid reaction. Suspension of both radial pulse and respiration may occur so that the patient seems dead This reaction is indistinguishable from true arsphenamine collapse following the use even of a properly prepared preparation.

If the patient who receives acid arsphenamine is not dead when reached, a determined fight should be made for his life. When dilute acid solution has been administered, the outlook is excellent if alkalinization with Fischer's solution (p 387) intravenously is immediately employed. Intracardiac adrenalin and artificial respiration may keep the patient alive long enough to permit of its administration. Adrenalin should also be given intravenously if the heart is still acting. In two instances of arsphenamine collapse of the idiosyncratic type the determination to fight the case by these methods saved the patients lives. After the fourth hour anuria is apt to be recognized in patients who have not been completely alkalinized by vein. It will respond usually only to the use of Fischer's solution and large amounts of alkali by mouth, and per rectum. Warmth and supportive measures are, of course indicated.

Blunders (2)—Toxification of Drugs.—This has been to some extent discussed under technic. The shaking and aeration of neoarsphenamine in the process of preparation undoubtedly is responsible for a great deal of everyday trouble (see p 299) (*cf* mapharsen) The relative instability of neoarsphenamine demands, moreover that the preparation be kept in the dark and in an ice-box (which it seldom is) even by the distributor after it leaves the manufacturer Dissolving arsphenamine (606) with hot water and administering it immediately after preparation, increases the toxicity

Blunders (3)—Hurry and Speed.—The great toxifier of most intravenously administered medication is speed in injection, as has been repeatedly emphasized. The atmosphere of hurry is fundamentally inimical to the reactionless treatment of syphilis and must be systematically discouraged in office and clinic When even the busiest physician enters his treatment room he must leave behind for the moment all preoccupation with other patients and the affairs of his office and in a leisurely and premeditated fashion follow an exact routine to the completion of the treatment. The rates of injection appropriate to the intravenously administered arsenicals are given on page 269

Blunders (4)—Water Errors.—These have been discussed on page 268 Chills and fever occurring in crops among the patients given treatment on a certain day or following the administration of a drug not usually producing such reactions, warn the head of a service that technical exactitude is not being fully satisfied on this point.

Blunders (5)—Tubing Reaction.—These reactions occur in crops with a quite typical symptomatology This type of reaction must be specially guarded

against in the apparatus used for intravenous drip therapy They are due to a toxic substance soluble in weak alkalis, present in rubber vulcanized by certain methods associated with an excess of sulphur The substance is removable from new tubing by soaking in 5 per cent NaOH solution for twenty-four hours. The reaction was described by Busman and Stokes and was evidently an occasional source of "trouble epidemics" in the First War In from thirty minutes to an hour after injection an increasing weakness with aching of the legs and back is noted followed by a chill, often of great severity The chill may be the first symptom Nausea and vomiting occur with violent cramplike pain in the lumbar region and diarrhea with tenesmus. Headache is intense and with repetition of the rigor there is a sharp rise in temperature the fever reaching from 102° F to 103.5° F accompanied by varying emotional disturbance and prostration Patients frequently laugh and cry hysterically The temperature then usually declines to normal within eight hours but the fever may persist for two or three days and the headache, backache, gastro-intestinal disturbance and prostration may persist for several days to a week. A profuse crop of herpes often follows the reaction. We have seen one case of jaundice but no renal complications. Considering the extremely pronounced and unpleasant character of the symptoms, recovery in robust persons is rapid and complete.

It is conceivable that the reaction in the debilitated or when coupled with Herxheimer effect or an intolerance of arsphenamine, might have serious consequences. What was apparently fatality from this cause was reported to one of us (J H. S.) by physician after the publication of Busman and Stokes observations. Busman developed a leukocytosis of 14,600 with 91 per cent polymorphonuclears at the height of the fever while Stokes had white count of 9600 with 82 per cent polymorphonuclears Both urines were normal. The pulse is likely to remain rapid for several days. Important symptoms may fail to appear or may assume unusual severity The general features of the reaction, however run so true to form both in man and dog that they suggest the toxic action of definite poison, possibly one of the mercaptans, since the reaction seems to occur chiefly in sulphur vulcanized tubing In large hospital services the reaction can usually be recognized as group affair involving considerable number of patients whose course under treatment has been previously uneventful. Guy in his report of reactions at Camp Travis, describes group of complications of unknown cause affecting 33 patients treated in single forenoon, which was identical in all respects with the tubing reaction. Even after the publication of Stokes and Busman s observations, group of tubing reactions appeared on the Mayo Clinic service following the advent of an inexperienced nurse.

The tubing reaction requires only symptomatic treatment, the recovery usually being uneventful.

Blunders (6)—Embolism.—Embolism must be regarded as a blunder at least in intravenous work, though the explanation may fail to materialize. Agglutination of red cells in speed shock may conceivably induce embolic effect. Clearing a plugged needle by running a stylet through it while the point is still within the lumen of the vein is another known source of embolism. Air embolism, often feared, is in our experience a trifling matter for it is remarkable what amounts of air can pass into the cubital vein without symptoms of any sort from the patient, albeit with impending nervous collapse on the part of the inexperienced operator who sees the bubbles go through the glass telltale too late to shut them off While proper attention to filtration is necessary Loren Shaffer undertook to inject intravenously in rabbits fluids containing considerable amounts of suspended cotton fibrils and so forth without at any time producing symptoms suggestive of embolism. Breakage of a needle within the lumen of the vein with lodgment of the fragment in the heart has

been said to occur In all probability the larger part of the symptoms even remotely suggestive of pulmonary embolus including pain in the side, pain in the chest and dyspnea following intravenous injections (6 in 6500 injections) is due to agglutination thrombi due to too rapid injection rates Shivers finds that precipitation of all the arsphenamines occurs in the blood *in vitro* at a pH below 6 4

Small pulmonary emboli should be symptomatically treated by rest in bed and local topical applications if signs of pleurisy develop. Pneumonia may ensue. It is not always advisable to silence the cough. Cerebral emboli are usually fatal. Emboli in other structures may give no signs except perhaps localized pain and a slight rise of temperature, their identification as emboli being therefore only speculative and *post hoc* Burns and Bromberg have reported a fatal case of cerebral embolus following the injection of arsphenamine in a woman of fifty-one in which the clinical symptoms suggested hemorrhagic encephalopathy and the gross autopsy appearances seemed to confirm the diagnosis. On microscopical examination however multiple fat emboli were found in the brain kidneys and lungs.

Following intramuscular injection, emboli may occur with or without fault in technic. A violent fit of coughing beginning while the patient is still on the table or shortly after he rises, is the commonest sign. In some cases syncope may occur and cerebral embolus may be fatal Technical factors are subsequently discussed.

Local Arterial Embolism —Arterial embolus into the skin following insoluble intramuscular injections gives rise to a very characteristic group of symptoms, according to Freudenthal who reported the first observed cases from Jadassohn s clinic, and Gammel who reported the complication in the American literature. It occurred, in Gammel s experience, five times in 45 000 injections. From a few minutes to a few hours after the withdrawal of the needle through which an insoluble bismuth or mercurial preparation (or other than antisyphilitic drugs, Sulzberger and Baer 1940) has been injected the patient complains of pain often severe and usually radiating down the leg The buttock swells rapidly the infiltration appearing more superficial than the deep resistance of abscess formation. There may be symptoms referable to nerve injury such as a dead feeling in the foot, in the bladder region and so forth and in 4 of the reported cases the symptoms of peroneal paralysis have appeared. Freudenthal gives it as highly characteristic that the symptoms are not only local as in irritation dependent on the site of injection but that the patient feels sick all over" and may have fever If the arterial tree is involved at the proper point, lesions of the bladder and vagina may appear The highly characteristic external manifestation is the retiform network of a bluish color which forms over the buttock from the eighth hour to the first or even second day There may be a slight tendency to gangrene in the darkened meshwork or massive gangrene of the rectum bladder penis scrotum and vagina may occur as reported in Gammel s and Kimberly s (1938) cases, for example

The process must be distinguished from local anaphylactic reaction to bismuth in which there is swelling and edema of the buttock but no network and no referred pain deep abscess which is much slower in developing, not usually accompanied by constitutional symptoms, and presents only deep induration without referred pain and deep hematoma which does not give rise to the retiform network, gangrenous changes and constitutional reactions

The milder examples of arterial embolism recover uneventfully on rest and

hot applications. *If gangrene occurs, the slough must be allowed to separate* or be surgically removed (Gougerot) The very slow granulation resulting from the impaired blood supply would, one might expect, be stimulated by the use of sulphhydril (Sulfen) Nerve injury if it occurs, recovers quite slowly and there may be residual paralysis.

The prevention of this unfortunate accident is not wholly dependent on the aspiration technic advocated on page 305 in intramuscular injections. Gammel points out that an attempt to aspirate through a small needle filled with a heavy emulsion will fail to detect the presence of a needle point in a vessel and that emboli of this type may also result, when the injection is given into the wall of a vessel and not into the lumen proper (Freudenthal) Gammel recommends as special precautions either the use of an empty needle, which is aspirated by a separate syringe before the syringe containing the emulsion is attached, or the use of a needle proportionate in size to the heaviness of the emulsion, the largest sizes being used for the heaviest emulsions. In any case, it is impossible absolutely to insure against the occurrence of this accident and this point should be borne in mind in medico-legal considerations.

Infection —The occurrence of systemic infection from unclean technic must be excessively rare. It may however result from the neglect of certain considerations other than those of mere asepsis. The lowered resistance of diabetic patients and their susceptibility to pyogenic infection, or of elderly patients in a cachectic condition may lead to meningeal infection by passing through infected tissue in entering the spinal canal or following even the proper injection of an intramuscular suspension. Infections of the meninges may follow the withdrawal of spinal fluid in patients with a septicemia, which emphasizes the great importance of the detection of intercurrent infections prior to any such procedure in treatment work. The mere presence of pus in a localized abscess after intramuscular injection does not prove infection nor does the grumous bloody fluid that may occur from the saponification of a bismuth compound in the tissues with swelling of the buttock and localized tenderness indicate infection or poor technic. The remarkable safety factor involved in all manipulations in which blood and blood serum are concerned is nowhere better illustrated than in intraspinal therapy in which, in spite of a technic that can be only relatively aseptic in the bacteriological sense because of the impossibility of complete sterilization, infections are rare (1 in 10 000 injections, in our experience) In procedures involving the treatment of patients with donors serum the possibility of transfer of infection must be considered

THE CONTROL OF COMPLICATIONS IN TECHNICAL PROCEDURE

Needle Complications.—In Figs. 181 and 182 are tersely summarized the prevention and management of that highly disagreeable and sometimes serious group of accidents due to needle breakage. Their technical importance is, like the function of the stable door less often thought of before than after

Intramuscular Injections.—In the technical description of intramuscular injection procedure, the impression might be gathered that uniform smoothness of performance is the rule. In Figs. 183 184 and 185 are summarized the preventive and treatment aspects of the complications of this technical procedure. Forethought, asepsis, inspection, placement, aspiration, and massage make up the "art" of intramuscular injection Forethought inquires into the results of the previous treatment and the condition of the tissues especially

Multiple nodules mean accumulating drug or poor technic and vehicle. Edema and tenderness with orange or grapefruit-like masses in a large, fatty buttock, may mean abscess formation, cystic accumulation or saponification (Barthelmy) Abscess may be entirely asymptomatic and point only after several weeks or even months or it may require evacuation within a few days. Hem

Fig 181

TO PREVENT NEEDLE BREAKAGE

1 Use only the latest nonbrittle noncorrodable steels. Watch for inferior material and workmanship in wartime
2 Have the needle point sharp.
3 Never jab or force against an obstacle
4 Test needles for condition especially if used with corrosive drugs (Hg soluble) (Fig 105)
5 Guard against sudden movement of the patient whether of back, muscle twitch, etc. Explain to him what is about to happen.
6 Guard the holding hand from sudden movements (pp 305 323)
7 Never introduce a needle all the way to the hub Leave at least ¼ inch exposed.
8 Avoid changing hands on syringes with needles fixed in tissue.

atoma and suggillation give rise to no serious difficulties. The discoloration is not retiform or netlike but diffuse and "black-and-blue" fading to yellow An infiltration is not necessarily below the needle point but may appear at the outer edge of the buttock. Diffuse gradual fibrosis (fesse de bois of the French) produces at first a doughy rubber-ball firmness, ultimately with a

Fig 182.

IF A NEEDLE BREAKS

If an intramuscular needle breaks:
1. Silence. Admit no blame. Stub and syringe kept out of sight.
2. Keep left hand in place. Feel lightly for fragment if broken near surface (hub)
3. If not felt, let go with hand.
4. State facts to patient after reflection, witness present.
5. Sometimes worth while to try to recover fragment through small incision under local anesthesia. Only if palpable in the skin.
6. Take patient to roentgenologist and surgeon for visualization, plates (2, 90 degrees) and removal of fragment.
7 I moving, avoid all weight or pressure on site.
8. Keep the fragments as recovered, with the hub and plates.
9. Write full account into the history t nce.
10. Notify insurance protection Move f release only on their advice.
11. If spinal needle breaks, proceed bove but
 ( ) Maintain patient' posture on table. Keep spine sharply flexed.
 (b) Do not lose the puncture site in local sterilization. Mark and note landmarks.
 ( ) Call the surgeon to the case
 (d) A oid crushing the needle ith hemost ts

woody or almost gritty fibrosis on pa ing the needle and a return or leakage of the injected su pension.

Placement into any but the upper outer quadrant may give rise to nerve injury as in Gammel's case of peroneal nerve injury by a medical student. Freudenthal points out that injection toward the outer in tead of the inner part of the outer quadrant is more likely to m ol e the arterial plexu *in local em-*

bolism. Aspiration and the selection of a needle large enough to pass easily a suspension of the viscosity employed will reduce emboli to the lowest terms. A fluid vehicle given through too large a needle may cause leak-back with infiltration. Massage is discussed on page 307

Technical Trouble in Intravenous Injection Causes and Treatment.—For purposes of condensation and reference the causes and treatment of primarily technical difficulties in intravenou injection are described under the following seventeen heads

1 **Pains at injection site during injection** Caused by (*a*) dull, overlarge or lacerating needle which strips vein (*b*) striking a "pain per

Fig 183.

TO AVOID TROUBLE IN INTRAMUSCULAR INJECTION

1 Use noncorroding needles.
2 Test by bending strain at frequent intervals (Fig 103)
3. Insist on asepsis (by boiling of instruments, p. 256 *et seq*)
4 Warm and shake suspensions thoroughly (p 301)
5 Be sure solubles are completely dissolved.
6. Question the patient before injection (p 381)
7 Palpate the buttock for nodes, tender spots, fluctuation.
8. Inspect the mouth nd skin.
9 Introduce clea needle no drug on the outside Empt needle or large-bore needle for heavy suspensions.
10. Be quick but don't jab. Watch corsets.
11 Use long enough needle for fat patients (p 293)
12 Use the upper outer quadrant of the buttock (Fig 181)
13. Aspirate by pulling back on the piston after introducing the needle Count 10 slowly (Fig 168)
14 Inject slowly
15 Hold needle in place one minut after injection.
16. Utilize valve action t prevent leak-back by pushing skin and subcutaneous tissues upwards after needle is ithdrawn (for thin suspensions and solutions)
17 Massage site one t three minutes or more
18. Have patient exercise his gluteal muscles after treatment.
19 Insist on hot sitz bath and massage daily (p 383)
20. If needle breaks—be silent and see Fig 182.

FORETHOUGHT ASEPSIS, INSPECTION PLACEMENT ASPIRATION MASSAGE MAKE UP THE ART" OF INTRAMUSCULAR INJECTION

ception point (*c*) leakage of irritant solution (*d*) striking or impaling a nerve (median) (*e*) hematoma

Treatment ( ) hold needle still without torsion or ten ion, while injecting (*b*) use local anesthetic (see p 312) ( ) stay within antecubital space if possible (*d*) avoid injection of deep structures out of sight and feel (*e*) secure full return of blood before injecting

2 **Perivenous tissue infiltration** Caused by ( ) nonentry (*b*) partial entry (see Fig. 134) (*c*) vein tear (*d*) bstruct on of thin-walled vein above site (*e*) injecting through a hemat ma.

Treatment: ( ) stop (*b*) inquire (patient may think it *should* hurt) ( ) withdraw (*d*) choose new site elsewhere and complete injection (to avoid sensitization) ( ) cold wet compress or ice-bag—after

twenty four hours hot magnesium sulphate solution compress (f) local or intravenous injection of sodium thiosulphate solution, if

Fig 154.

TREATMENT OF INTRAMUSCULAR INJECTION COMPLICATIONS

1 For prevention, see Fig 153
2 Palpable induration or pain.
 ( ) Question correctness of site
 (b) Avoid node or change buttocks.
 ( ) Both sides involved—consider postponing
 (d) Paint sit with tincture of iodine (if no skin irritability)
 ( ) Inquire int nd insist on sits bath, heat nd massage
 (f) Massage more thoroughly after injection
 (g) Reduce dosage especially for first 4 injections I patient ho has had no intra muscular treatment.
 (h) Increase local anesthetic if used
 (i) Cha ge t another preparation.
3. Twinge down leg.
 ( ) Change site before injecting (farther up and out)
4 Pain down leg.
 ( ) Question sit of injection
 (b) If pronounced, skip one treatment or change side
 ( ) Heat, salicylates by mouth, baking infra-red radiation
 (d) Look for other causes of sciatica, especially focal infections.
5 Aspiration yields fresh blood.
 ( ) Withdraw needle without injecting Choose new sit 2 cm. ay Preferably change sides.
 (b) If much blood, use fresh needle fresh drug
6 Aspiration yields pus (or old bloody fluid)
 ( ) Silence t the patient.
 (b) Leave needle in, ttach fresh syringe aspirate as much as possible
 ( ) Hot pplications and expectancy Absorption is the rule
7 Severe suggillation, cutaneous embolus.
 ( ) Absolut rest N massage.
 (b) Ice-bag. Later hot compresses.
 ( ) Morphine.
8 Drug leaks back.
 ( ) Smaller bore needle
 (b) Hand valve action.
 ( ) Keep needle in place one minut
 (d) Massage
 ( ) Hot pplications and sits bath
 (f) If buttock fibrous, suspend tre tment
9 Systemic embolus
 ( ) Bed, quiet, ice-bag symptomatic treatment.
10. Abscess.
 ( ) Allow t t seven day for localization
 (b) Drain through small incision under local nesthesia. N pack or drain usuall necessary
11 Broken needle.
 See Fig 152

much edema or necrosis threaten (g) massage baking, pas ive movement.

3 **Necrosis and slough** Caused by (a) large amounts or concentrated alkaline 606" or "914" (b) other alkaline solutions (Fischer s)

Treatment (*a*) ice-bag, later heat (*b*) dry treatment until slough is defined (*c*) piecemeal excision (*d*) sulphhydryl wet dressings (*e*) massage, electric light exposures, baking passive movement.

Fig 184.

TECHNICAL TROUBLE IN INTRAVENOUS INJECTION

1. Pain at injection site.
2. Perivenous tissue infiltration.
3. Necrosis and slough.
4. Hematoma.
5. Suggillation and subcutaneous hemorrhage.
6. Pain in shoulder or arm during injection.
7. Vein spasm.
8. Thrombophlebitis (acute).
9. Thrombophlebitis (chronic, local)
10. Entering an artery
11. Broken needle.
12. Bleeding puncture.
13. Discoloration of site.
14. Puncture tattoo.
15. Injecting median nerve.
16. Cutting down on vein.
17. Speed shock.
18. Embolism.

EVEN THE BEST OPERATORS HAVE ACCIDENTS

4 Hematoma Caused by (*a*) transfixing of vein (complete puncture of opposite wall) and partial withdrawal (*b*) withdrawal after entry but no return of blood (plugged needle or transfixed vein) (*c*) torn vein (thin wall, dull needle) (*d*) leaving tourniquet on after withdrawing needle.



Fig 185 —Slough following the injection of neoarsphenamine int the subcutaneous tissue The entire arm from below the elbow to above the middle of the biceps is brawny and the elbow is immovable Evidently almost the entire dose of concentrated solution had been delivered outside the vein.

Treatment compression bandage at site, elevation of arm when bleeding stops, cold compress. Complete the injection elsewhere.

5 Suggillation and subcutaneous hemorrhage Caused by (*a*) blunt needles which tear or round instead of pointed needles which, in

stead of puncturing, cut (b) too large needle (c) thin veins (d) no compression on withdrawal (e) blood dyscrasia.

Treatment (a) pressure bandage (b) reassurance (c) better technic (d) hypodermic needles (26-gauge) in syringe technic.

6 Pain in the shoulder or arm during injection Caused by (a) hyper alkaline "606" (b) other irritant solutions (c) vein spasm (q v) (d) slow injection of mapharsen

Treatment (a) quantitative alkalinization (b) slower rate or intermittent injection (c) salt solution 0 6 per cent as solvent (see p



Fig 187 —Result of injecting the median nerve with arsphenamine, mistaking it for vein (patient right arm) *The unhealed slough, nearly year old, can be seen above the inner condyle* There is distinct trophy of the muscles, loss of power in the hand, atrophy of thenar eminence, and trophic ulcer on the anesthetic index finger

260) (d) slapping lightly over vein (spasm) (e) hot applications (f) calcium gluconate solution, 10 per cent 10 cc. by very slow intravenous injection just before treatment (hypodermic needle) (g) injecting mapharsen rapidly

7 Vein spasm Caused by (a) idiosyncratic hypersusceptibility (b) other causes as for pain (above)

Treatment (a) as for pain (b) change of drug

8. Thrombophlebitis (acute) Caused by (a) idiosyncrasy (b) alkaline or irritant solution (c) slow injection of mapharsen Symptoms (a) pain at time of injection or spasm (b) tenderness, slight redness bruise discoloration along vessel (c) closure in four to seven days

(d) fibrous bluish-white cord thereafter or may reopen, but vessel rarely usable again.

Treatment Usually none Hot compresses.

8a. Thrombophlebitis (chronic) Caused by repeated injections into same vein, with slow cordlike obliteration or nodosity at site.

Treatment alternation of veins, saline solvent, drug-change good technic.

9 Entering an artery Caused by aberrant course of brachial artery Symptoms: spurt of bright blood or syringe piston forced out of barrel.

Fig 186.

PREVENTION OF SPINAL PUNCTURE REACTION

1 Know in advance that no increase in intracranial pressure exists (symptoms of headache vomiting, and finding of choked disk)
2. Take temperature and inquire for symptoms of respiratory and other infections.
3. If any trace of blood appears, keep patient in bed for twenty-four hours.
4 Use relatively small needle (21 or 22-gauge)
5 Take pressure with manometer if possible Normal for Hg 7 12 mm., for water 100–180 mm.
6. Allow fluid to drip very slowly Never aspirate (A flow of 1 to 2 drops second is safe)
7 Give sedative (codeine, 1 grain hypodermically or sodium amytal 3 to 5 grains thirty to forty minutes before puncture) with dose to take home.
8 If ambulatory have patient rest one hour on stretcher face down, then go home until next morning.
9 Patients who return to heavy work do so at their own risk.
10. If rest can be secured, four to six hours sleep after puncture is advantageous.
11 Patient may go to stool or urinal. No straining If unable to pass urine report by telephone.
12. Report pain in legs, weakness, stiffness, spasticity fibrillary twitchings, by telephone
13. If headache develops, lie down, have someone report by telephone Remain quiet, foot of bed elevated forty-eight hours.
14. Mild saline cathartic day following puncture if constipated
15 No rough jouncing travel, forty-eight hours.
16. Medullary block (abrupt cessation of respiration) and hemorrhage symptoms may be *delayed six to twenty-four hours. Report as under 13.*
17 Recent, as yet unevaluated, observation suggests that reaction may actually be prevented by exercising the patient or allowing him to be active after lumbar puncture. Not yet recommended.

Treatment withdraw if using gravity method, inject if not. Compression over puncture two to three minutes.

10 Broken needle (See p 396, Fig 182)

11 Bleeding puncture Caused by entering skin and vein in same movement. See also No. 5

12. Discoloration of site (permanent) Caused by (a) perivenous leakage of certain drugs such as colloidal mercury sulphide, silver salts (local argyria) gold salts.

13 Puncture tattoo Caused by: (a) droplet of colored solution on needle when entered (b) rusty needle or corrosive solution ($HgCl_2$)

14 Injecting median nerve Caused by (a) technical ignorance (b) hit or miss probing out of sight or feel. Symptoms (a) twinge and pain down arm to fingers (b) later atrophy etc. (see Fig. 187)

Treatment as for (9)

15 Cutting down on vein unnecessary in present-day practice
16 Speed shock Caused by (a) inexperience (b) hurry See page 244
Symptoms nitritoid reaction gastro-intestinal reaction etc.
Treatment See page 410 small needles, timing device, vigilance.
17 Embolism Caused by (a) "ramming" a plugged needle with a stylet while in vein (Baketel) (b) "mauling" a fat arm or leg with a

Fig 189

TREATMENT OF SPINAL PUNCTURE REACTIONS

1 Headache (and nausea)
(a) Prevention (see Fig. 188)
(b) Reassurance
(c) Lie down without pillow The headache stops.
(d) Remain lying down (in bed) twenty-four to forty-eight hours. (No attempts to rise to see if "it is passing off")
(e) Quiet.
(f) Foot of bed elevated 6 to 10 inches.
(g) Patient fed lying down.
(h) Enema or mild laxative as needed.
(i) If headache does not pass off on lying down, seek other explanation—most often rheumatic or indurative headache with occipital stiffness and localized tender points relieved by infra-red radiation and massage
(j) If patient must be up, or after second day in bed, give capsule of phenacetin 3 grains, acetylsalicylic acid 2 grains, caffeine (stimulant) or sodium bromide 3 grains (sedative) as indicated every two to four hours.
(k) Failure to clear the bowel after puncture may result in nondescript headache
2. Retention of urine
(a) If longer than twelve hours, and no pain, twitchings, altered reflexes, or other signs, allow use of stool Take temperature
(b) Avoid catheterization. Try hot packs, posture etc
(c) In lower cord tabes and myelitis symptoms may not be noted for several days.
3. Stiff back.
(a) Reassurance
(b) Heat or infra-red radiation.
(c) Capsule as for headache
4. Hemorrhage
(a) If early warnings, ice-bags, absolute quiet morphine
(b) Laminectomy drainage if level signs high
5 Meningitis (infectious).
(a) Diagnosis by fever leukocytosis, lack of level signs (extensive process)
(b) Puncture for diagnosis. Coincidently meningococcus serum intraspinally
(c) Double puncture drainage and lavage
(d) Forced drainage—hypertonic saline intravenously with spinal drainage (Kubie-Casten)
(e) Neurological consultation.
6. Traumatic neurosis ("railway spine")
(a) Eliminate organic possibilities.
(b) Reassurance and firmness.
(c) Galvanism and other treatment for hysteria

blunt needle and tearing the vein (c) acid arsphenamine (d) severe nitritoid (see p. 410)

Prevention and Treatment of Spinal Puncture Reaction.—We have attempted to summarize the prevention and treatment of spinal puncture reaction in Figs. 188 and 189 for convenience of reference The technic appropriate to these considerations is given on page 518

Pseudoreactions.—These include indurative headache and stiff neck not relieved on lying down and due to the so-called "rheumatic" torticollis or fibrositis. The identification of the characteristic tender nodes in the nuchal and suboccipital region is seldom difficult and the response to infra-red radiation and massage usually good. Hysterical puncture headache with rigidity of the neck when the canal has not even been entered, has occurred in our experience and responds to suggestive therapeusis and reassurance.

DRUG REACTIONS AS SUCH

The Mouth.—The mouth is one of the most important structures in the whole reaction field. Some form of involvement of it occurs with varying frequency from all the drugs used in the treatment of syphilis, being most frequent with mercury and bismuth and least so with iodide. Mouth reactions are not necessarily a symptom of overdosage, as is often supposed, but may be an expression of idiosyncrasy, especially to arsphenamine and iodide. The appearance of mouth lesions, diffuse or localized, is not to be looked upon as an isolated phenomenon but as part of the systemic toxic reaction to the drug in question, to be dealt with as a symptom of general reaction rather than as a merely local phenomenon. On the other hand, as in all manifestations of intolerance, the weakest point of resistance yields first, and by proper prophylaxis may be bolstered up to carry a heavier load for the sake of the general therapeutic end in view.

Properly heeded, the mouth together with the skin furnishes early warnings of a number of the gravest complications in the treatment of syphilis. It is inexcusable to allow the ordinary case under treatment to reach the extreme degrees of reaction. For that reason we have included weekly inspection of the mouth in all preventive suggestions and have summarized in Fig. 190 the warnings which the mouth gives of impending or actual trouble, together with associated groups of symptoms arranged under the drug from which they may be expected.

It is impossible to escape the impression gained by comparing the course of numbers of patients under careful mouth prophylaxis and that of those under indifferent management, that the bacterial influence in the production of stomatitic complications weighs more than any other factor except the accumulation of detritus which provides for the nourishment of a rich saprophytic flora in ill-kept mouths.

Stomatitis may occur in small groups of patients, apparently due to a common infection epidemic at the time rather than to the technic of treatment. A striking example of this was noted by one of us (J. H. S.) at the Mayo Clinic where in November 1919 an epidemic of tonsillitis *was associated with a wave of severe stomatitis, in spite of the usual precautions, in those* under mercurial treatment.

The oral hygiene appropriate to the general treatment of syphilis has been outlined in Fig. 175, and with its use the stomatitic manifestations, primarily of local origin as with bismuth and mercury, should become comparative rarities. A number of differential points, however, deserve emphasis. A heavy metal stomatitis and gingivitis is the product of the deposit of sulphide of the heavy metal about the capillaries of the mucosa. Edema, bleeding, lividity of the tissues and discoloration by the deposit, most marked in the case of bismuth, are features of all cases. The patchy, irregularly distributed pigmentation of the mucosa under bismuth treatment is relatively rare in moderate dosage and American authors have been inclined from their experience to

minimize bismuth stomatitis especially as rarely constituting a serious difficulty in ordinary dosage. On the other hand, with mercury stomatitis (Fig 191) is so common an occurrence that it is even regarded by some as a guide to therapeutic saturation and almost a goal to be reached With this point of view we take issue, considering the renal index of irritation the only safe one to employ In a case of nearly fatal accidental mercurial poisoning the renal

Fig 190

MOUTH WARNINGS OF TROUBLE
With Associated Groups of Symptoms
(Numerically Arranged in an Average Order of Appearanc)

From Arsphenamin
1 Dry red mouth.
2. Chapping lips.
3. Bleeding from the gums (not "pink toothbrush")
4. Purpuric stippling of gums or mucosae or outright hemorrhages, breaking dow to form ulcerations.
5 Marked exaggeration of pyorrheic ymptoms, or appearance of "trench mouth.
6. Gangrenous points, especially t sites of pyorrhea pockets.
7 Warning symptoms of bone marrow injury—fall in leukocytes, rise in eosinophils, drop in platelets.
8. Malaise, pallor itching of the skin, purpura.
9 Agranulocytic angina with gangrene.
From Bismuth.
1 Fetor (foul breath) A important early sign.
2. Blue line t gingival margin (look behind upper incisors)
3. Bluish spots in gums or mucosa (bisulphide) especially near third molars, cheeks, and tonsillar pillars.
4. Aching discomfort on clenching the ja ("bit test")
5 Edema of gums and tongue (especially around third molars)
6. Beginning "trench mouth
7 Gangrenous points or exudate around pyorrhea pockets.
8. Massi gangrene (with agranulocytosis).
9 Local adenopathy
From Mercury
1 Aching discomfort on lenching the ja ("bite test")
2. Swelling of gum flap over third molar makes biting painful at that site.
3. Edema of tongue and gums (especially recognizable bout third molars, pyorrhea pockets, nd imprints of teeth in sides of tongue)
4 Local adenopathy (submaxillary)
5. Increased flow of sali
6. Bleeding of gums.
7 Erosions and exudat gums and tongue.
8. Localized gangrenous points. Does not produce agranulocytic picture in mouth and throat
9 Mercurial pallor cachexia, anorexia, arthritis.
From Iodides.
1 Metallic tast (unimportant)
2. Possible occasional exaggeration of existing stomatitis.
3 Bullous and purpuric lesions (extreme iodism)
4 Parotid edema (iodide mumps)
5 Laryngeal edema nd iodide laryngitis.

symptoms reached a high degree of severity while it was still possible to control the stomatitis by a careful prophylaxis. In the extreme grades of mercurial stomatitis, involvement of the tonsils, pillars, soft palate and pharynx may be so severe as to simulate a Vincent s infection In fact, it is important to realize that Vincent s infections may be stimulated or even precipitated by such minor mercurialization as 2 grains of hydrargyrum cum creta by mouth

Peters (1942) has commented on the lack of attention given to the associ

ation of bismuth stomatitis and albuminuria. He collected from the files of the Johns Hopkins Hospital 6 cases of bismuth nephrosis or albuminuria with severe ulcerative stomatitis and 7 with a similar but mild complication.

Arsenical stomatitis (Fig 192) as we have seen it differs quite sharply from heavy-metal stomatitis in the dry red, glistening appearance of the mucous surfaces as distinguished from the lividity and exudative characteristics of heavy-metal stomatitis. There is, moreover no pigmentation unless the patient coincidently is taking bismuth A grave sign in all stomatitic conditions is the appearance of necrosis and of submucosal hemorrhage This warns not only of the severity of the stomatitis as such but of the development of agranulocytosis under arsphenamine or bismuth therapy or the onset of aplastic anemia. So important are these considerations that the appearance of a well-marked stomatitis of any type calls for a complete blood count with a study of the blood smear for the hematological signs of damage to the hematopoetic mechanism (Fig. 194) One should not wait until itching and eruption or purpuric hemorrhage appears. Stomatitis associated with pharyngitis and tra



Fig. 191 —Beginning mercurial stomatitis developing at the base of lower central incisor Note the early warning of the submental adenopathy The patient as taking inunctions

cheitis is an accompaniment and sometimes a warning of the onset of exfoliative dermatitis and its appearance is therefore a signal for the discontinuance of the arsphenamine until the situation can be evaluated. In general, it is a warning of a serious grade of idiosyncrasy to the arsenicals. The clean, dry hot, red, exfoliative characteristics of a stomatitis point to the arsenical factor although in occasional cases the bacterial flora of a gum pocket may start a secondary process resembling a heavy metal stomatitis and amenable to the same treatment.

Treatment of Stomatitis.—The intake of heavy metal or arsenical should at once be stopped and immediate investigation made to determine whether the stomatitis is associated with hematopoietic changes or not. If these blood studies are negative and the patient is taking mercury by inunction or is in a room with a patient who is taking inunctions, he should be placed in another room and if receiving inunctions, should be given two hot soap-and-water baths and a sweat (wet pack) If the heavy metal has been given intramuscularly in cumulative form there is nothing to do but fight it out, and every

effort should be made to keep up the patient's nutrition and spare his kidneys by rest in bed, a bland diet rich in carbohydrate in the case of heavy metal poisoning, fats and proteins if the hepatic complications of an arsenical injury appear. Alkalinization should be carried out, milk taken in abundance and sodium thiosulphate may be given in 0.5–1 Gm. doses intravenously every second day for 3 to 4 injections. Calcium gluconate intramuscularly 10 cc. of a 10 per cent solution may also be used every second or third day. The care of the mouth calls for the separation of the gums from the cheeks and the tongue from the teeth by thin strips of cotton soaked in boric acid solution or liquor antisepticus alkalinus, frequent changes of the cotton strips, a mouth wash every two hours of liquor antisepticus alkalinus containing ½ per cent zinc chloride or Dobell's solution, which has a comforting anesthetic effect, and the attention of a dentist to the gum pockets is very helpful, if available. In fact, in severe cases skilled dental aid is worth all the other measures combined and will control the most resistant tendency to relapse (*cf.* McCarthy and Dexter 1935).



Fig. 192.—Stomatitis produced by arsphenamine. There was no general reaction except dry angina.

In addition to the foregoing measures some assistance in dealing with the gangrenous lesions of agranulocytosis may be obtained by the use of ultraviolet light locally with the Kromayer lamp and dental applicators. In these cases, when due to the arsenicals, we are inclined to avoid the use of an arsenical even locally in the treatment of the stomatitic process. We have no personal experience with the use of vitamin C (Marin, 1942) and sodium hexametaphosphate (Felsher and Jones, 1941) as a dentifrice (15 per cent Na hexametaphosphate and 85 per cent talc) in the prevention of or treatment for bismuth stomatitis and pigmentation.

A severe attack of stomatitis as a local manifestation seems to predispose to relapses and mouth prophylaxis should be strictly adhered to while the heavy metal is very cautiously resumed. The caution about acid foods in the oral hygiene summary (Fig. 175) must be taken seriously. Sensitive persons have noticed effects from the eating of a single sour apple.

There is a distinct tendency on the part of the arsphenamines given intravenously to diminish the incidence of heavy metal stomatitis, probably through their effect on the Vincent flora. For this reason, if the patient is on heavy metal alone, neoarsphenamine may be resumed intravenously and a 10 per cent solution in glycerin also applied locally to the gums. A 10 per cent

hot sodium perborate solution is preferable to the packing of these Vincent mouths with powdered sodium perborate provided the solution is used hot and frequently under proper direction.

Iodide stomatitis in our experience is a very great rarity probably because it is usually cloaked by the ascribing of the cause to a heavy metal simultaneously administered. Of iodide pharyngitis and laryngitis we have seen only one case but the possibility should be kept in mind in giving treatment to laryngeal lesions, in which serious edema may be induced.

Gastro-intestinal Reactions.—The general preventive aspects of the control of the gastro-intestinal reactions have been presented in Fig. 176, page 380. Gastro-intestinal reactions to the arsenicals range from slight anorexia with or without nausea to intractable vomiting lasting for several days, and from a sequence of two or three rather voluminous stools on the night following an injection to a profuse watery diarrhea. In some cases the gastric symptoms particularly are associated by the patient with the disagreeable ether or garlic-like odor which he notes at the time he is receiving the injection particularly in the case of neoarsphenamine. The disagreeableness of this experience may start the train of gastric reactions in hypersensitive persons. There is also a close clinical relationship between the nitritoid vascular crisis and subsequent gastro-intestinal reactions, and the methods advised for the control of acute vascular reaction (p. 410) have decided value in reducing the tendency to gastro-intestinal reaction. We therefore regard the marked parosmia experienced during injection, the tendency to vascular reaction and the gastro-intestinal phenomena as part and parcel of the same reaction mechanism and are placed on our guard by their repeated recurrence accordingly. For the disagreeable odor and taste many patients experience great relief from allowing a peppermint, clove, or wintergreen wafer to dissolve on the tongue during the injection.

Vomiting on the table occasionally occurs in nitritoid crisis, but is usually the result of faulty preparation of the patient (see Fig. 193, p. 410). Nausea alone makes up the large proportion of late reactions during the ensuing twelve hours. About 60 per cent of patients receiving intensive drip arsenotherapy experience it, most severely on the first day. For this reason, where possible, it is advisable to give the drug in the morning so as not to disturb the patient's sleep. Most patients feel well enough by evening to protest if their meal is made too light. Those who vomit more than once should be given 2 glasses of warm water with a drachm (not a teaspoonful) of sodium bicarbonate. This is usually vomited again and the patient feels much relieved. If vomiting or nausea persists, cracked ice, chewed and swallowed (not melted in the mouth), an ice-bag to the pit of the stomach (sometimes a hot water bag is preferred), and carbonated water or ginger ale poured over cracked ice, will often relieve. Obstinate vomiting, lasting several days, sometimes responds to cold buttermilk and a good beer is occasionally specific. Arsenicals have a disagreeable trick at times of precipitating the gastric crises of tabes dorsalis and repeated severe vomiting should be carefully considered from this standpoint if the case is one of neurosyphilis. On very rare occasions gastric lavage may be employed or hypodermic sedatives necessary (codeine rather than morphine should be used). The onset of a jaundice is sometimes predictable from the recurrence of gastro-intestinal reactions or the unusual persistence of any given episode after treatment. Close attention should be paid to the sclerae and the urine.

early syphilis must be recalled If the fever lasts longer than twelve hours, the Herxheimer effect is practically excluded. The macular type of toxic eruption is faintly visible over the chest, abdomen and flanks, and fades within one or two days without desquamation. The papular type usually appears within forty-eight hours, is confined largely to the hands and arms and is often associated with the arthritis of the smaller joints that constitutes the so-called "arthritic reaction." The morbilliform or measly eruption is abundant and extensive the macules retiform and at times confluent over the trunk and extremities. This seldom appears before the third day and is strongly suggestive of measles except for the absence of Koplik's spots and coryza. At times there may be some dryness and redness of the mucous membranes and a cough which with edema of the lower lids and engorgement of the conjunctivae, may make the resemblance to measles marked enough to be deceptive. Some residual pigmentation or a slight furfuraceous desquamation may follow The scarlatiniform postarsphenamine erythema has a febrile prodrome usually shorter than the morbilliform type. A scarlet blush appears first on the face and extremities, spreading in varying degrees over the entire body There is sometimes considerable associated edema and the eyes may be swollen shut. There is however no exudation and the color remains bright instead of becoming livid or bronze as in true exfoliative dermatitis. The subsidence of the erythema about the third to fifth day is followed by a rather abundant, large, flaky desquamation and the palms and soles may peel in casts strongly suggestive of those seen after scarlet fever Mouth symptoms and angina are rare and we have never seen a suggestion of strawberry tongue This form of arsphenamine erythema is, in appearance, a close approach to exfoliative dermatitis and we personally believe that we have seen evidence of its passing over into exfoliative dermatitis after a lull or intermission (Fig. 197)

I fifty-two of Peters fifty-four patients there ere dermatologic manifestations. There was no correlation between the size of the dose and the occurrence of the syndrome. Fifty-two patients had two or more injections of the drugs before its appearance Over 70 per cent of the patients had general lymph node enlargement, enlarged palpable cervical nodes and tonsillar hypertrophy some had conjunctival suffusion. Hepatomegaly was noted in nine patients, and jaundice in seven. The syndrome lasted six days, excluding patients who became jaundiced, five days for the erythema and one day for the prodrome. There were no fatalities.

The immediate associated reactions, integral features of the syndrome, were mainly visceral and occurred in 24 per cent of this series. There were eight patient ith "hepatitis, four with hepatomegaly alone, two with nephritis and one each with splenomegaly alone and granulocytopenia. Delayed complications, caused by further treatment with the arsphenamine drugs, occurred in 43 per cent of thirty-six patients and consisted of dermatitis (all types), recurrent erythema of the ninth day nitritoid reactions, fever gastro-intestinal reactions and intolerance to the usual trivalent arsenicals. Of all patients receiving further arsenical preparations, 70 per cent had reactions. Of fifteen patients who had reactions to arsenical drugs prior to the occurrence of erythema of the ninth day 60 per cent developed serious sequelae to treatment after its occurrence.

In general, the blood smears showed shift to the left, and in severe cases there as mild leukopenia of the granulocytic series with relative monocytosis or lymphocytosis. Eosinophilia of 5 per cent or greater appeared in 44 per cent of patients. Of this group, 67.5 per cent had serious immediate manifestations or subsequent treatment complications, while of the patients with eosinophilia of 0 to 4 per cent, only 35 per cent had reactions. The likelihood of serious immediate or delayed complications increased with the degree of eosinophilia. Among patients receiving further arsenotherapy during or within two weeks of onset of the prodrome 77 per cent had serious complications, while of those who received treatment later than two weeks, only 23 per cent had complications and these were relatively mild. There ere two instances of infectious relapse of the syphilitic disease in this series. Peters concludes that the erythema of the ninth day syndrome predisposes to infectious relapse of the syphilitic infection when arsenotherapy is

hot sodium perborate solution is preferable to the packing of these Vincent mouths with powdered sodium perborate, provided the solution is used hot and frequently under proper direction.

Iodide stomatitis in our experience is very great rarity probably because it is usually cloaked by the ascribing of the cause to heavy metal simultaneously administered. Of iodide pharyngitis and laryngitis we have seen only one case but the possibility should be kept in mind in giving treatment to laryngeal lesions, in which serious edema may be induced.

Gastro-Intestinal Reactions.—The general preventive aspects of the control of the gastro-intestinal reactions have been presented in Fig 176, page 380 Gastro-intestinal reactions to the arsenicals range from slight anorexia with or without nausea to intractable vomiting lasting for several days, and from a sequence of two or three rather voluminous stools on the night following an injection to a profuse watery diarrhea. In some cases the gastric symptoms particularly are associated by the patient with the disagreeable ether or garlic like odor which he notes at the time he is receiving the injection, particularly in the case of neoarsphenamine. The disagreeableness of this experience may start the train of gastric reactions in hypersensitive persons. There is also a close clinical relationship between the nitritoid vascular crisis and subsequent gastro-intestinal reactions, and the methods advised for the control of acute vascular reaction (p. 410) have decided value in reducing the tendency to gastro-intestinal reaction. We therefore regard the marked parosmia experienced during injection, the tendency to vascular reaction and the gastro-intestinal phenomena as part and parcel of the same reaction mechanism and are placed on our guard by their repeated recurrence accordingly For the disagreeable odor and taste many patients experience great relief from allowing a peppermint clove, or wintergreen wafer to dissolve on the tongue during the injection.

Vomiting on the table occasionally occurs in nitritoid crisis, but is usually the result of faulty preparation of the patient (see Fig. 193, p. 410) Nausea alone makes up the large proportion of late reactions during the ensuing twelve hours. About 60 per cent of patients receiving intensive drip arsenotherapy experience it, most severely on the first day For this reason, where possible, it is advisable to give the drug in the morning so as not to disturb the patient's sleep. Most patients feel well enough by evening to protest if their meal is made too light. Those who vomit more than once should be given 2 glasses of warm water with a drachm (not a teaspoonful) of sodium bicarbonate. This is usually vomited again and the patient feels much relieved. If vomiting or nausea persists, cracked ice, chewed and swallowed (not melted in the mouth) an ice-bag to the pit of the stomach (sometimes a hot water bag is preferred) and carbonated water or ginger ale poured over cracked ice, will often relieve. Obstinate vomiting, lasting several days, sometimes responds to cold buttermilk and a good beer is occasionally specific. Arsenicals have a disagreeable trick at times of precipitating the gastric crises of tabes dorsalis and repeated severe vomiting should be carefully considered from this standpoint if the case is one of neurosyphilis. On very rare occasions gastric lavage may be employed or hypodermic sedatives necessary (codeine rather than morphine should be used) The onset of a jaundice is sometimes predictable from the recurrence of gastro-intestinal reactions or the unusual persistence of any given episode after treatment. Close attention should be paid to the sclerae and the urine.

Diarrheas may be said to begin arbitrarily with more than 3 stools following an intravenous injection. Postarsenical diarrhea rarely lasts more than a few hours and should not be too hastily controlled by constipating measures such as opiates, since this closes an important channel of elimination. The patient who has had 3 or 4 stools, however should not be given a cathartic unless the trouble persists, in which case 1 or 2 tablespoonfuls of castor oil may be used. Dietary error and improper preparation should be inquired into. Placing the patient for several days or a week on a very soft diet with much heavily buttered milk toast (the milk should be boiled) will sometimes do away permanently with irritability of the bowel under arsenical treatment.

Hematemesis and melena after the arsenicals occasionally occur in patients who have gastric or duodenal ulcer or without any demonstrable lesion of the gastro-intestinal tract. Painless vomiting of blood and the passing of tarry stools may begin a few hours after an arsenical injection. The patient should be put to bed with morphine and an ice-bag and immediate preparations made for transfusion, if necessary If an ulcer was previously demonstrated, a surgeon should be called at once The accident is fortunately very rare Melena may also occur quite without warning and sometimes in grave proportions following the rupture of a varix in the stomach secondary to an unsuspected or underestimated cirrhotic process in liver or spleen.

Abdominal Pain after Arsenical Injection.—In contradistinction to mercury which more frequently gives rise to abdominal pain, the arsenical gastro-intestinal reactions are generally painless and the occurrence of the symptom of pain suggests the possibility of gastric crisis or of an intercurrent cause such as infectious diarrhea. We have seen one case of perforative peritonitis following arsphenamine in a patient with syphilis and gastric ulcer in which immediate surgical intervention saved the situation. Symptomatic vomiting from abdominal complication must always be borne in mind and the reaction should not be considered casually Vomiting forms part of the syndrome of acute yellow atrophy after arsphenamine, but jaundice and hepatic enlargement usually precede it. The abdomen should always be carefully examined for signs of an acute abdominal process, the mere fact that the patient has had arsphenamine never being allowed to cloud the judgment or obscure the possibility of a surgical complication. This is especially true of patients with organic gastric lesions, such as ulcer

The nitritoid reaction has a marked gastro-intestinal phase (see p 391) but the onset is characteristically with a chill and sudden rise in temperature which is quite diagnostic. Vomiting also occurs in severe therapeutic shock and is part of the prodrome of a toxic erythema (ninth-day erythema, see p 419)

Gastro-intestinal Symptoms after the Heavy Metals.—In this respect mercury is the principal offender and the advent of bismuth has been a great relief to the often hard-pressed physician and patient. A certain amount of anorexia, often pronounced, is an almost invariable accompaniment of mercurial therapy but the combination of this form of treatment with the arsphenamines gives a much-needed tonic effect. Perhaps one patient in a hundred cannot take mercury by mouth without trouble, mercury with chalk being in our experience the best tolerated. Patients on inunction rarely have gastro-intestinal difficulties, but the mercurial intestinal symptoms, particularly diarrhea, are more often associated with insoluble mercurial salts. An ordinary looseness of the bowels can be controlled in heavy metal therapy by soft diet and boiled milk. Milk toast is particularly effective. The sudden diarrhea which follows at times the injection of either an insoluble or more often a soluble salt may be controlled by a drachm or two of paregoric after each stool for 2 or 3 doses, and rest in bed. A powder of bismuth subgallate with charcoal, 30 to 60 grains of each suspended in water or milk may be given

every four hours. Bloody diarrhea with tenesmus requires an ice-bag to the abdomen and rest in addition to the above measures and a dose of morphine hypodermically is sometimes necessary although its use should, as always, be a last and not a first resort. Careful inquiry after a heavy-metal diarrhea has nearly always pointed to an indiscretion in diet, especially the eating of a large amount of fresh fruit. No permanent intolerance usually results from these sporadic disturbances. Chronic diarrheas (persisting more than four days after the heavy metal is stopped) should not be too readily accepted as of drug origin and treated in merely palliative fashion. The emotional factors in diarrhea, especially with much mucus in the stools, must be considered and achlorhydria likewise, though it is difficult to deal with it while the patient is on heavy metal therapy. The stools should be microscopically examined for parasites and blood and the possibility of an infectious diarrhea or dysentery and of chronic ulcerative colitis considered. Proctoscopic examination sometimes discloses an ulcerative proctitis which may require local treatment and large, hot, saline irrigations. The colonic ulceration of severe heavy metal poisoning requires similar measures.

Constipation during heavy metal therapy is usually corrected by the coincident use of the arsenicals, but in the case of mercury taken by mouth may be obstinate and trying. The use of a mild alkaline laxative usually deals with these cases satisfactorily. A warning should be issued against the use of cathartics.

Mercurial colic which is reduplicated symptomatically in susceptible persons by iodide colic, though there seems to be no homologous reaction to bismuth in our experience, seems to be an actual idiosyncrasy to the drug and consists of abdominal pain or cramps, suggesting almost the pain of intussusception or acute obstruction without diarrhea and even with obstinate constipation. There may be diffuse abdominal rigidity and some distention but no localizing signs. Hot packs to the abdomen and turpentine stupes may give some relief but the recurrence of the trouble when the drug is resumed usually forces suspension of the form of treatment responsible. Rectal tenesmus, possibly localized expression of the same condition further down the tract, is occasionally solitary symptom after intramuscular mercurial injection but in our experience has not constituted serious obstacle to treatment.

The bismuth enteritis is a relatively rare complication in ordinary dosage and this makes bismuth the logical heavy-metal resort in patients with hypersusceptible gastro-intestinal tracts. Gastro-intestinal reactions occur however in one third of patients receiving sobisminol by mouth. Cramps, probably of iodide origin, occasionally occur after iodobismitol intramuscularly.

Vascular Reactions to the Arsenicals.—Vascular reactions are here distinguished from reactions in the hematopoietic system, which are separately considered as the next topic. The outstanding vascular reaction to antisyphilitic treatment is the nitritoid crisis. In the light of what we now know of the mechanism of this type of reaction, the outstanding cause must be considered a defect in technic—namely the too-rapid administration of intravenous medication. On the other hand, nitritoid crisis is known to occur after intramuscular injections of bismuth and bismuth-arsphenamine combinations and even after foreign proteins such as boiled milk. It rarely occurs, however after injections of mapharsen which is administered rapidly. The disturbance of the colloid balance may therefore be induced by a number of factors and is subject to a certain extent to a general preventive and treatment mechanism.

The warnings of vascular reaction are summarized in Fig. 193. Vascular reaction usually develops while the patient is "on the table" but it may be

Fig. 183.

WARNINGS, PREVENTION AND TREATMENT OF THE NITRITOID VASCULAR REACTION

and its Correlated Gastro-intestinal, Pruritic, Asthmatic, and Urticarial Reactions

Warnings:

1. For their recognition these require the exposure of patient neck and arm t the shoulder face in full view
2. In the first stag the earliest signs are as follows
   ( ) A deep breath or two.
   (*b*) Gulping t or three times in succession Watch the larynx.
   ( ) An xpression of anxiety or restlessness.
3. Th second stage begins with
   ( ) Suffusion of f ce and neck or red blotching Thi is late sign and will almost alw ys go on t full reaction, requiring adrenalin treatment.
   (*b*) Deep, apoplectic flush nd edema of the face and neck with or without urticaria nd flushing over the bod
   ( ) Choking.
   (*d*) Wheezing and stridor (asthma")
4. The third stage incl des
   ( ) Unconsciousness, pupil usuall dilated, eyes open.
   (*b*) Pulselessness and collapse (rare)
   (*c*) Slow recovery is the usual rule

Prevention

1. Slow injection of properly prepared drugs (see p 900) or use of mapharsen.
2. Attention t the empty stomach rule
3. In known susceptibles (including vagotonics") use seriatim the following
4. Atropine ¼ t grain hypodermically t enty t thirty minutes before injection.
5. Besredka immunization or ntianaphylaxis —give ¼ the full dose slowly intravenously follow by the remaining in forty minutes.
6. I syringe technics (10-cc volume) keep the tourniquet on for t or three minutes.
7. Use special solvent (glucose vitamin C)
8. Use (4) nd (5) combined.
9. For succeeding injections, if no contraindications, give preparation 50 mg ephedrine in capsule the night before and agai one hour before injection.
10. *Rout nely place such patients on calcium by mouth, 60 grain of the gluconat t to* three times daily
11. Give lcium gluconat intramuscularly 5 t 10 cc of 10 per cent sterile solution (ampule) one-half t one hour before injection
12. Change t nother drug only if thera se uncontrollable
13. A similar preventive regimen pplies t gastro-intestinal reactions, pruritus (as solitary symptom) urticaria and asthma after rsphenamine treatment
14. The tendency t vascular reaction nd it correlates may disappear spontaneously but repetition ith increasing severity in spit of preventiv measures is arning of seriou intolerance

Treatment

1. Stop the injection If recognized in the first stage keep needle i vei five minutes, try resuming injection very slowl If not or symptom recur ithdra nd proceed as in (3) nd (4)
2. Epinephrine solution 1 1000, 10 minims hypoderm lly ll massaged In severe reactions additional 5 t 10 minims ntravenousl if heart intact.
3. Reassure the patient.
4. Severel reacti ng patient require bed, alkali zat on, ttention t gastro-intest nal symptom

STOP NITRITOIDS AT THE START

delayed ten minutes or more and o ertake him on his way out of the office or treatment room in which case it has an unforgettable effect on anyone who

happens to witness it. In the delayed reactions following bismuth and bismuth arsphenamine sulphonate intramuscularly more than half an hour may elapse before the crisis develops and the symptoms are correspondingly more protracted alarming and, inasmuch as they usually take place on a street car or in a corner drug store disturbing to the equanimity of the patient and the reputation of the physician. The absent minded operator who does not watch his patient during the injection abruptly comes to a realization of the situation after the stage indicated in 2, Fig 193, which is the proper time to recognize a nitritoid crisis, is passed. In occasional cases the reaction may be fulminating in rapidity From the subjective standpoint the experience is a terrifying one for the patient, accompanied by a sense of suffocation and impending death which makes him very loath indeed to repeat the experience. The consequences are rarely serious if the injection be stopped on the first warning sign, but if the reaction is fully developed before it is observed by the operator it may be so serious as conceivably to cause death in weakened individuals with serious organic lesions. We have never however seen or encountered a record of death from true nitritoid crisis. The reaction, with its attendant gastrointestinal sequelae may cause miscarriage in pregnant women, as in the case recently reported by Halloran.

Prevention and Treatment of Nitritoid Reactions.—This is summarized completely in Fig. 193. An occasionally used preventive is the addition of 5 minims of 1 1000 epinephrine solution to each 100 cc. of injected solution (especially "606") but Lees found the combined atropine-antianaphylaxis preferable. Dissolving the arsenical in a vitamin C containing solvent (methyl glucamine ascorbate) may at times prevent the reaction

The relation between the severe gastro-intestinal reaction as species of sequela of the nitritoid crisis was recognized by Beeman, who pointed out the applicability of the same methods of treatment to both conditions. By combinations of antianaphylaxis and atropine alone without ny of the later added methods it was possible to carry number of patients who had developed marked reactivity which ould have been sufficient to force discontinuance of treatment, through their normal schedules.

Differential Diagnosis.—The nitritoid crisis must sometimes be rapidly differentiated mentally in the treatment room from conditions which may resemble it, including colloidoclastic shock (arsphenamine idiosyncrasy and bismuth intravenously) arsphenamine collapse cardiovascular collapse convulsive seizures (epileptic, eclamptic, hysterical) and manifestations of fear anxiety embarrassment, and minor hysteria. Colloidoclastic shock associated with acid arsphenamine administration and so-called "arsphenamine collapse" differs sharply from the nitritoid crisis as it develops, in that in shock the patient is pale, pulseless and collapsed, while in the typical nitritoid he is flushed, hyperactive, coughing, choking and with a bounding pulse that may later momentarily collapse. The complaint of pain in the back is rarely heard in nitritoid crisis and frequently in shock or collapse. Cardiovascular collapse produces a greenish pallor or cyanosis with dizziness, sweating low pulse and feeble heart sounds in marked collapselike contrast to the florid redness, coughing, wheezing and agitation of the typical nitritoid. The true epileptic convulsion is of course easy to recognize but petit mal may be more difficult, though it usually lacks the flush and vascular reactivity the patient simply muttering or mumbling, passing into unconsciousness with some ticlike movement, and presently regaining consciousness without treatment. An eclamptic

seizure is a tonic convulsion without striking vascular manifestations, the clenching of the jaw and convulsive rigidity being very striking Major hysteria is momentarily perplexing but the rigidity the catatonic state and particularly the symptom of holding the thumb rigidly across the palm, makes differentiation usually possible. Any hypodermic medication usually brings about an immediate recovery The flush and restlessness of simple agitation and minor hysteria become easily recognizable on knowing the mental and nervous state of the patient, though one or two experiences may be necessary to a definitive diagnosis. A search should always be made for definite stigmas of hysteria in patients showing reactions of this type Naborro believes the nitritoid reaction markedly influenced by psychic disturbances, although its rarity after mapharsen tends to lay the blame for nitritoid reaction on the drug

Other Vascular Reactions.—Mercury practically never produces clinically recognizable cardiovascular reactions as ordinarily employed in treatment. Bismuth we have seen given before cardiac collapse which may of course,have been *post hoc*. Attacks of paroxysmal tachycardia and occasionally bradycardia may be precipitated by the arsenicals in patients who have been subject to them. The effect of this group of drugs on the heart circulation is well illustrated by its tendency to bring on angina pectoris in patients with impaired coronary circulation, a consideration that must not be lost sight of in therapeutic tests. Management of such cases with reference to arsenical treatment is discussed in detail in Chapter XIX. The localized injury to the capillaries of the brain which forms the basis of serous apoplexy or hemorrhagic encephalopathy is described on pages 244 434

Cardiac death after arsenicals without any technical fault or idiosyncrasy can nearly always be traced to preexisting cardiac disease, usually syphilitic in character and especially involving the coronary vessels. This, with the effect of the therapeutic shock (Herxheimer) on aneurysm with resultant rupture and death is also fully discussed in Chapter XIX Complications of this kind can only be forestalled by careful study of the patient before treatment is begun and by great caution in the use of the arsenicals and practical exclusion of arsphenamine (606) in serious late cardiovascular lesions

Purpura and extensive capillary hemorrhage after an injection of an arsphenamine is a sign of the gravest import, and should be a warning never to repeat this form of treatment. Such a reaction is part of the picture of hematopoietic injury considered on page 413 The effect of arsphenamine on blood pressure discussed on page 244 has lost clinical interest, but the blood pressure of the pregnant woman should be taken before each intravenous injection as a means to detecting the onset of the intoxications of pregnancy

Acute cardiac accidents on the table should be treated with 0.5 to 1 cc. adrenalin solution 1 to 1000 subcutaneously or intravenously or if collapse is complete and no heart rate detectable with the stethoscope, by the intracardiac route Two to 5 cc. are injected into the ventricle in the fifth interspace about 2 cm. to the left of the sternal border Aspirate first, to be sure the ventricle has been entered A wait of two or three minutes after the intravenous injection of adrenalin is permissible, however inasmuch as these patients are sometimes not as dead as they seem and revive under artificial respiration in that length of time. A report by Bodon (see also Champlin) of revival after apparent death from syphilitic coronary arteritis, encourages the belief that this method may be used in acute accidents from this cause occurring following arsenical treatment

Reactions of the Hematopoietic System.—Current conceptions as to the rarity of this group of reactions would probably require modification if periodic blood examinations were made of patients showing malaise pallor pruritus and purpuric manifestations under arsphenamine treatment. Aplastic anemia causes 5 per cent of postarsenical deaths. It seems very probable that some degree of bone marrow injury comparable perhaps in frequency to hepatic injury from the arsenicals could be detected in this way Duke pointed out (Bronfin and Singerman) that the same group of fundamental injuries is capable of expressing itself in one patient by progressive anemia, weakness and prostration with a slow fatal outcome in a second with agranulocytosis and *subsequently infection, notably angina* when there is failure of regeneration of leukocytes and in still a third group in purpura with hemorrhage *when there occurs a considerable diminution in the blood platelets.* Some diminution with subsequent increase, according to Jui-Wu Mu follows the ordinary administration of neoarsphenamine, especially if there is fever

Fig 194

WARNINGS OF INJURY TO THE HEMATOPOIETIC SYSTEM
(Aplastic Anemia, Purpura, Agranulocytosis)

1 A history of hemophilia, anemia, hemorrhages, etc.
2. Evidence of general reactivity especially repeated severe nitritoids and gastro-intestinal reactions.
3. Pallor weakness.
4 Purpuric spots on gums, mucosae, skin of abdomen, wrists, ankles. Numerous *suggillations or unexplained "bruises.*
5. Bleeding gums. Mucosal hemorrhages.
6. Subconjunctival hemorrhage.
7 Epistaxis.
8. Hematemesis.
9 Black stools.
10. Stomatitis with *fetor*
11. Gangrene in the mouth or throat.
12. The blood count Drop in reds, normal or low color index, leukopenia, drop in granulocytes, rise (relative) in lymphocytes, drop in platelets, drop in reticulocytes, absence of immature forms normal to an anemic blood picture (Bronfin and Singerman).

The warnings of injury to the hematopoietic system are summarized in Fig. 194, and in the preceding résumés of preventive procedure emphasis has been placed on the steps necessary to detect them. Periodic blood counts of all patients who do not do well under treatment would in all probability be the most effective preventive device. Moore and Keidel and Moore and Foley extended the search for warning blood changes to the necessary prophylaxis of other forms of reaction, particularly dermatitis, pointing out that the changes found differed only in degree rather than in kind from those which marked the fatally reacting aplastic case. Semenza has also stressed the prophylactic value of periodic blood counts. Sternal puncture may be of value in certain cases not only to determine the fact of depression of bone marrow function but also for differential diagnostic purposes. Determination of the icterus index or Van den Bergh reaction may be of value in early detection of potential hematopoietic damage.

The onset of the aplastic process which results in one or other of the three groups of symptoms classified by Duke may begin within from twelve to

forty-eight hours after the injection It may follow the initial dose or any subsequent dose. Slowly progressive weakness and pallor may precede the hemorrhagic manifestations or the development of stomatitis by one or two weeks. In some cases, nitritoid reactions of increasing severity seemed to form a prodrome. Sometimes there appear a few purpuric spots on the lower extremities or abdomen a day or two after the injection preceding the fatal one

The clinical course is usually rapid, nonremittent and lasts rarely more than two or three weeks, although the so-called "primary or idiopathic types of aplastic anemia," according to Schneider have an average duration of six months. The tendency to early hemorrhagic manifestations is quite characteristic. Slight epistaxis slight bleeding from the gums, or an insignificant conjunctival hemorrhage may be the first symptom to alarm the patient sufficiently to bring it to the attention of the physician We have thought that easy bruising of the skin and the appearance of large black and blue spots, different from the small purpuric hemorrhages seen on the extremities and minimized by the patient on the ground that he always "bruises easily may have prodromal significance. As the disease progresses, bleeding from the mucous membranes becomes a prominent symptom. Fever is a common accompaniment, dependent in part on the proportion that the agranulocytic mouth symptoms and pulmonary complications bear to the picture as a whole Abdominal pain without hepatic or splenic enlargement is said by Bronfin and Singerman to accompany the cases with hematemesis and melena. The purpuric spots appear and fade in groups over the upper extremities and chest and there may be marked traumatic suggillations over the elbows and sacrum and erosive changes where heavy bleeding takes place into the mucous membranes. The prognosis is grave from the outset, but in our experience, patients who survive the fifth day have at least a fighting chance for life, though the term is a misnomer in view of the ineffectiveness of practically all therapeutic procedure In the more prolonged cases the great thing to be feared is intercurrent infection which closed the picture in one of our particularly hopeful experiences after some weeks of steady favorable progress under antianemic measures. Stephens noted beginning bone-marrow regeneration in one of his two cases.

The purpuric type of hematopoetic reaction may give rise to a very confusing picture simulating hemorrhagic encephalopathy as in the case reported by Lasersohn in which fatal hemorrhages took place into the brain and spinal canal as well as the mucosae skin, and viscera. In fact the terminal picture in a purpuric aplastic case may be that of cerebral hemorrhage rather than death from infection

The treatment of the hematopoietic group of complications consists first in immediate and probably absolute discontinuance of an arsenical when even traces of purpura have appeared in the patient. Mapharsen may at the hands of the expert be cautiously used as a substitute in exceptional cases. We do not, however favor this procedure. Sodium thiosulphate has been advised but should certainly not be continued beyond the three injections repeatedly mentioned Calcium in large doses by mouth and theoretically at least, intramuscularly would seem rational but one hesitates at the intramuscular administration particularly where there is a definite tendency to hemorrhage Fibrinogen thromboplastin coagulen, have been of no avail in the cases we have seen. Vitamins P K, and beef thrombin, while mentioned are as yet unevaluated or untried Scarborough (1940) and Gorrie (1940) secured what

they believed to be recoveries in hemorrhagic purpuras secondary to arsenic and bismuth but according to Quick (1942) the results were not sufficiently controlled to be trustworthy in view of the tendency to spontaneous recovery. Antivenin was used by Bronfin and Singerman in their cases without effect and Semenza found splenectomy of no avail in one case. In several of our patients with hemorrhagic purpura Koagamin (an oxalic acid containing extract of certain plants) intravenously was beneficial (Steinberg, Segal and Parris 1940). Blain and Campbell (1942) showed that a sterile aqueous solution of recrystallized oxalic acid intramuscularly was useful to control bleeding. The optimum dose was 20 mg. Every effort should be made to build up or stimulate the activity of the bone marrow by antianemic measures of the type employed by Minot, Castle and their co-workers, including the administration of large doses of liver extract (pernicious anemia fraction) without iron or liver extract administered parenterally. The dose should be large rather than small. Where agranulocytosis is marked, as in patients with severe stomatitis and angina pentose nucleotides may be tried. Jackson, Parker, Rinehart and Taylor benefited two cases of benzol poisoning as well as other cases of malignant leukopenia, by the use of this preparation (NNR). Burke also found this to be of value. We have used leucocytic cream (transfusions of blood from leucemic patients) with probably good effect. Burke thought such transfusions of decided benefit. In cases associated with marked blood loss from hemorrhage the Whipple fraction of liver with iron may be used. In addition, cod liver oil in large doses should be given or the anti-infection vitamins A and B in the form of halibut liver oil, a brewers' yeast extract or other B complex preparations and vitamin C. We have not tried vitamin P. Irradiation of the patient with the carbon arc or sun lamp (not necessarily short wave ultraviolet) and the sedulous exclusion of all sources of infection from visitors and so forth is imperative. The administration of hydrochloric acid and of extracts of gastric mucosa or whole stomach must be governed by the indications under the guidance of an expert hematologist. All things taken together, we have felt that the small transfusion (250 cc.) frequently repeated, has probably as high a sustaining value as any single measure. Occasionally unfavorable reactions seem to ensue, but are probably merely part of the course of the complication.

The steady decline of the foredoomed case only too often illustrates our fundamental helplessness in the face of an inevitability dependent on biological exhaustion or ruinous intoxication of an essential structure like the bone marrow.

The lack thus far of evidence of unfavorable effect from simultaneous use of two hematopoietotropic drugs has been mentioned but deserves further study. The injury involved seems highly specific for the individual drug.

Syphilis complicated by pernicious anemia furnishes a special problem in treatment and the prevention of reactions which was studied by several authors, including Fouts and Stokes. The tremendous modification of the prognosis and treatment of pernicious anemia since this study makes a reinvestigation of the whole question desirable but one or two points still deserve emphasis. Bismuth is preferable, of course, to mercury as a heavy metal in such cases and neoarsphenamine preferable to arsphenamine (606). It would seem that bismuth arsphenamine sulphonate could have a field of usefulness here. Transfusion should be a preliminary to arsenical treatment when the hemoglobin is below 50 per cent but under present practice liver therapy will, of course, be used coincidently or antecedently. Reactions to arsenical injections must be carefully avoided since they may produce an alarming drop in hemoglobin. No satisfactory rule for determining which case would improve on treatment for syphilis and which case would not, can be arrived at, about half the cases improving under the older regimen. Frequently repeated blood counts are necessary as indices of progress.

Hepatic Complications.—The causal mechanism is considered on page 248 and the differential diagnosis is discussed in Chapter XVIII because of its close association with the symptomatology of syphilis of the liver

In Fig 195 is presented a series of warnings of hepatic complications which, though more or less irrespective of the type applies particularly to intercurrent catarrhal or so-called "postarsphenamine jaundice" and the acute yellow atrophies. The rôle played by the liver in the economy of the patient with syphilis is so large that with the improvement of liver functional tests it would seem justifiable to employ them in an anticipatory way to recognize at least subthreshold bilirubinemia. All patients who are not doing well under treatment should be scrutinized for signs of hepatic difficulty including palpation of the liver enlargement of which may precede the onset of definite jaundice.

Treatment decisions must rest on a careful differentiation (see p. 248) of the possibilities involved. It is usually advisable to shift, even in an apparently

Fig 195

WARNINGS OF HEPATIC COMPLICATIONS

1 Evidence of general reactivity: severe nitritoids, gastric disturbances, patient not doing well.
2. Anorexia.
3 Abdominal discomfort or actual distress, rarely sharply localized.
4 Light stools (not necessarily clay colored)
5 Dark urine.
6 Bilirubinemia as indicated by icterus index.
7 Stiff joints (especially shoulders and back.)
8 Yellow sclerae.
9 Liver may or may not be palpable or enlarged at the start, may shrink in size (atrophy)
10. Fever
11 Deepening jaundice
12. Abdominal pain, liver tenderness, confusion, delirium or stupor prostration (acute yellow atrophy) May appear early usually late.

SOME LIVER INJURY PROBABLY ACCOMPANIES ALL TREATMENT WITH ARSENICALS, AND MAY BE SERIOUS

syphilitic icterus, from the arsenicals to bismuth and to push it with reasonable vigor for a period of weeks before returning to the arsenicals when the trouble has subsided The tendency for bismuth preparations to cause hepatic injury and jaundice should not be forgotten (Nomland, Skolnik and McLellan (1938) Gott and Doyle (1939) Lane (1939) Wolman (1940) Kulchar and Reynolds (1942)) O'Leary and Rowntree emphasized the seriousness of these cases from the standpoint of future embarrassment in treatment and the possibility of later hepatic complications. In early cases in which it is imperative to continue arsenical treatment this may be done provided the picture conforms to the catarrhal type, but neoarsphenamine or mapharsen should be substituted for arsphenamine and repeated blood counts taken to be sure that no arsenical injury to the hematopoietic structures is taking place General detoxification measures can also be carried on in these patients hand in hand with the treatment of the syphilitic infection. A large body of experimental and clinical evidence has been accumulating to show that the liver may be spared by a diet high in protein. Carbohydrate is beneficial though to a lesser degree while

a fat diet proves deleterious (cf Craven (1031) Schifrin (1032) Beerman (1934) Goldschmidt, Vars and Ravdin (1939) Miller and Whipple (1940) Messinger and Hawkins (1940) Johnson, Ravdin, Vars and Zintel (1940) Mann (1041) Ravdin, Thorogood Riegel Peters and Rhoads (1943)) The greatest degree of symptomatic relief, particularly in the catarrhal type of case, comes from duodenal lavage as used by Wilhelm from the Mayo Clinic service following the technic of Lyon This procedure is so useful and so entirely harmless that it is here quoted:

> The tip of the tube is placed on the tongue, close to its base and the patient is told to swallow During the act of swallowing, the tube is started gently down the esophagus and is passed until level of about 40 cm mid y between the first and second markings, is reached. At this level the stomach is washed with sterile water until the return is clear The patient is then instructed to lie on his right side, extending his right leg and acutely flexing his left knee and hip He is told to pass the tube t the rate of 1 inch every five minutes until the third mark (75 cm.) is reached. W know that the tube is in the duodenum by change in reaction of the aspirated fluid from acid to alkaline by the character of the duodenal juice, which is usually a pearly viscid fluid, in which floccules are suspended sometimes by the presence of bile; by slight tug when the tube is pulled gently and by seeing the tip beyond the pylorus at fluoroscopic examination. (This is not usually necessary.) The tube is removed by withdrawing it gently until the tip reaches the nasopharynx. The patient is then told t swallow and the tip is easily recovered
>
> When the tube is in the duodenum, the latter is washed first with water at 40 C. and about 100 cc. of saturated solution of magnesium sulphate is washed back and forth in syringe with capacity of 100 cc. for about ten minutes. The duodenal contents are then allowed to siphon out. This process is repeated three or four times at intervals of thirty minutes. The tube is then ithdrawn, the stomach being washed again at this time, and the tubing being repeated every other day From one to eight tubings may be necessary nd the striking good effect is often recognized following the first or second lavage

Hanger and Gutman (1940) confirmed the value of dealing with post arsphenamine dermatitis as an obstructive jaundice in their employment of serum phosphatase determinations and cephalin flocculation tests to differentiate the obstructive from the parenchymal injury cases. They base their recommendations on drainage of the biliary tract and the use of choleretics such as bile salt preparations and cholic acid derivatives in treatment.

In addition to these measures or in cases where they are inapplicable, glucose intravenously may be employed, as suggested under general detoxifying measures. Sodium thiosulphate is not particularly useful either in our experience or that of Colonel Harrison Appel and Jankelson (1935) found sodium dehydrocholate useful as a solvent for neoarsphenamine to protect the liver by improving arsenic elimination so that patients could continue therapy even in the presence of jaundice. During the jaundice a diet of milk, eggnog, toast and fresh fruit has seemed helpful, and an occasional mild course of calomel and sodium phosphate, with oxgall tablets as suggested by Eppinger to diminish the viscosity of the bile. Simici and Popesco found that insulin favorably affects the hyperbilirubinemia of "postarsphenamine jaundice and shortens the course of the complication. It also combats the tendency to emaciation.

In view of the apparent usefulness of liver extract in certain arsphenamine complications, including dermatitis (Spiethoff MacKee and Astrachan) its trial in toxic hepatitis seems fully justified, but we have no personal experience with it.

Acute yellow atrophy like aplastic anemia, has a hopelessness and an even greater unpredictability which makes it the rival of arsphenamine dermatitis

as a mortality factor on large services. The symptomatology is marked by an onset that may immediately follow an arsphenamine injection or be delayed for weeks or even months. Out of a clear sky the patient rapidly becomes jaundiced with associated intense abdominal pain, tenderness over the liver and great prostration. Drowsiness, stupor and coma supervene on delirium; fever is frequently present, the urine contains bile, tyrosin, leucin, and the liver at first large begins to decrease in size as coma sets in. Death may occur in from three days to a week or more and the conventional treatment by alkalis, sodium thiosulphate, fluids, glucose intravenously is rarely of any avail. As in acute arsphenamine poisoning, there may be associated both dermatitis and peripheral neuritis, and likewise aplastic anemic manifestations

Fig 194

WARNINGS OF TROUBLE WITH OR FROM THE SKIN

General.
1 A history of irritable skin—trouble with soaps, cosmetics, sunburn.
2. The seborrheic state—dandruff (marked) oily skin, acne (or its scars), presternal and interscapular patches of scaling dermatitis.
3. The allergic state—a history or symptoms of asthma, hay fever, repeated attacks of hives.
4 The "vagotonic" or "high-strung" nervous state—red face and neck, blue hands and feet, "inward nervousness."
5 A history of eczema, personal or familial
6. A history of known specific drug sensitivities. Local reactions to iodine, etc.
7 A high carbohydrate diet or alcoholism.
8. A heavy load of focal infections.
9 An acute infection or exposure to cold (Harrison)
10. Marked repeated vascular and gastro-intestinal reactions, evidence of poor tolerance in general, ... nervous irritability

Special.
1 Itching on the day following injection. Never disregard it, especially with (2)
2. Stippled red rash, flexures, face and neck. Transient at outset. Inquire for it
3. Edema of eyelids.
4. *Chill and fever following arsphenamine (eighth-day erythema)* with florid rash fourth to eighth day
5. Patches of dermatitis or "eczema," recent or long-standing. Examine extremities, groins, hands especially. May also be dermatophytic or examples of "fixed arsphenamine exanthem
6 Large subcutaneous suggillation and nontraumatic black and blue spot
7 Purpura, especially noticeable about flexures, wrist and ankles, abdomen, mucosae
8 Pallor
9 Jaundice.
10 Stomatitis (arsenical type)
11 Blood count. Rise in eosinophils, drop in leukocytes, erythrocytes, platelets, immature red cells in smears.

with hemorrhages. Mistaken operative interference in intercurrent catarrhal jaundice has been known to be followed by a fatal picture suggesting acute yellow atrophy. It is, furthermore, essential to differentiate acute yellow atrophy of arsenical intoxication from that of syphilis, the latter being fortunately extremely rare. The symptomatology is essentially identical. Positive serological reactions and no history of treatment usually accompany the syphilitic form.

The Cutaneous Reactions.—While the skin, because of its visibility and extent, displays a disconcertingly large variety of reactions to treatment for syphilis, their occurrence is fortunately a comparative rarity (one in one thousand injections on a hospital service) and only two of them, arsenical

toxic erythema and arsenical exfoliative dermatitis, are of great practical importance. The types of cutaneous reaction to arsphenamine, bismuth, mercury and the iodides have been considered respectively on pages 245, 200, 217 and 220. The causal mechanism underlying the dermatitic types of cutaneous reactions was discussed on page 254. It remains, therefore, to consider the clinical symptomatology and treatment.

General detoxification measures may be considered as called for in all cases, regardless of type. Most inflammatory responses in the skin have two distinct groups of causes, the predisposing and the exciting, and failure to give adequate attention to the predisposing element in one's concern with the exciting factor usually results in prolongation of the course and relapse. This is especially true of the various forms of dermatitis attributable to treatment. In Fig. 190 are arranged the warnings of trouble with or from the skin so that the general warnings are of the nature of predisposing causes or background for the symptomatic or special picture of the case. Growing knowledge of the field is tending to emphasize more and more the importance of cutaneous manifestations as expressions of a systemic rather than a local process with underlying injuries to the bone marrow, liver and vascular system as well as the excretory mechanism as the principal elements in the perverted metabolism leading to reaction.

Arsenical pruritus and urticaria may be treated by the use of adrenalin or ephedrine as previously described. A shift of drugs and sometimes no therapeutic measure whatever may bring about a disappearance of the symptoms. Pruritus should always be carefully investigated for its possible connection with dermatitis exfoliativa on the one hand, in which it may terminate, and aplastic anemia and liver injury, of which it may be a symptom. The use of calcium and glucose as a buffer may be helpful.

The Erythema Multiforme Group—Ninth-Day Erythema.—These are the acute cutaneous reactions identical with those to which the name "ninth-day fever" or "ninth-day erythema" is applied.

Since the original descriptions (Milian (1917), Stokes (1940)) this phenomenon has been studied particularly by Peters (1941), Drummond (1941), Cathcart and Thomas (1939); Epstein and Levin (1939), Goldman and Clarke (1939); Robinson (1938); Goldman and Werner (1936); Gordon (1936).

These reactions are usually associated with a prodromal chill and fever which according to the accepted European descriptions usually appear on the seventh to the twelfth day after the institution of arsenical, rarely bismuth treatment, thus presenting something apparently suggestive of an incubation period. The patients receiving massive dose arsenotherapy who develop secondary fever (64 per cent) and (about 46 per cent) an accompanying erythematous eruption are thought to be exhibiting manifestations of ninth-day erythema. The prodrome usually appearing within twelve to forty-eight hours after an injection (usually the second or third in American practice) consists of headache, backache, stiffness and malaise, sometimes with obstinate vomiting or diarrhea. A febrile reaction at this stage of treatment which lasts more than twenty-four hours after the drug has been administered will almost certainly terminate in a toxic eruption of some type, usually by the third or fourth day, the eruption taking a scarlatiniform, a morbilliform, a rubeoliform, a polymorphous or an urticarial aspect (Milian). The differentiation from a cutaneous Herxheimer effect in

early syphilis must be recalled. If the fever lasts longer than twelve hours the Herxheimer effect is practically excluded. The macular type of toxic eruption is faintly visible over the chest, abdomen and flanks, and fades within one or two days without desquamation. The papular type usually appears within forty-eight hours, is confined largely to the hands and arms and is often associated with the arthritis of the smaller joints that constitutes the so-called "arthritic reaction." The morbilliform or measly eruption is abundant and extensive, the macules retiform and at times confluent over the trunk and extremities. This seldom appears before the third day and is strongly suggestive of measles except for the absence of Koplik's spots and coryza. At times there may be some dryness and redness of the mucous membranes and a cough which, with edema of the lower lids and engorgement of the conjunctivae, may make the resemblance to measles marked enough to be deceptive. Some residual pigmentation or a slight furfuraceous desquamation may follow. The scarlatiniform postarsphenamine erythema has a febrile prodrome usually shorter than the morbilliform type. A scarlet blush appears first on the face and extremities, spreading in varying degrees over the entire body. There is sometimes considerable associated edema and the eyes may be swollen shut. There is, however, no exudation and the color remains bright instead of becoming livid or bronze as in true exfoliative dermatitis. The subsidence of the erythema about the third to fifth day is followed by a rather abundant, large, flaky desquamation, and the palms and soles may peel in casts strongly suggestive of those seen after scarlet fever. Mouth symptoms and angina are rare and we have never seen a suggestion of strawberry tongue. This form of arsphenamine erythema is, in appearance, a close approach to exfoliative dermatitis and we personally believe that we have seen evidence of its passing over into exfoliative dermatitis after a lull or intermission (Fig. 197).

1 fifty-t of Peters' fifty-four patients there ere dermatologic manifestations. There was no correlation between the size of the dose and the occurrence of the syndrome. Fifty-two patients had two or more injections of the drugs before its appearance. Over 70 per cent of the patients had general lymph node enlargement, enlarged palpable cervical nodes and tonsillar hypertrophy; some had conjunctival suffusion. Hepatomegaly was noted in nine patients, and jaundice in seven. The syndrome lasted six days, excluding patients who became jaundiced, five days for the erythema and one day for the prodrome. There were no fatalities.

The immediate associated reactions, integral features of the syndrome, were mainly visceral and occurred in 24 per cent of this series. There were eight patient ith "hepatitis," four with hepatomegaly alone, two with nephritis and one each with splenomegaly lone and granulocytopenia. Delayed complications, caused by further treatment th the arsphenamine drugs, occurred in 53 per cent of thirty-six patients and consisted of dermatitis (all types), recurrent erythema of the ninth day, nitritoid reactions, fever, gastro-intestinal reactions and intolerance to the usual trivalent arsenicals. Of all patients receiving further arsenical preparations, 70 per cent had reactions. Of fifteen patients who had reactions to arsenical drugs prior to the occurrence of erythema of the ninth day 60 per cent developed serious sequelae t treatment after its occurrence.

In general, the blood smears showed shift to the left, and in severe cases there as mild leukopenia of the granulocytic series with relative monocytosis or lymphocytosis. Eosinophilia of 5 per cent or greater appeared in 44 per cent of patients. Of this group, 87.5 per cent had serious immediate manifestations or subsequent treatment complications, while of the patients with eosinophilia of 0 t 4 per cent, only 35 per cent had reactions. The likelihood of serious immediate or delayed complications increased with the degree of eosinophilia. Among patients receiving further arsenotherapy during or within two weeks of onset of the prodrome 77 per cent had serious complications, while of those who received treatment later than two weeks, only 29 per cent had complications and these were relatively mild. There ere t instances of infectious relapse of the syphilitic disease in this series. Peters concludes that the erythema of the ninth day syndrome predisposes to infectious relapse of the syphilitic infection when arsenotherapy is

ithheld too long. N other effect on the course of syphilis w noted. The further administration of arsenical drugs should be withheld for at least one month following recovery from the reaction and should then be resumed cautiously ith small doses.

Part of the practical importance of the toxic erythemas aside from the discomfort they cause the patient lies in the reaction of the physician to the situation Milian has insisted that treatment can be continued after these reactions and we have personally confirmed this observation. On the one hand the hesitation of the physician in view of his proper fear of exfoliative dermatitis, is natural and a considerable hesitation and circumspection in resum-

Fig 197

TRANSITION TO EXFOLIATIVE DERMATITIS FOLLOWING ARSPHENAMINE NINTH-DAY ERYTHEMA

Association with Intercurrent Infection and Local Irritation (Inunctions)
Woman aged forty years, widow boarding-house keeper

10/22/20 **Entered Clinic with Maculopapular Secondary Syphilid** History of exposure duration of infection not known. Serum Wassermann reaction + + +
Cough Since Childhood, of increasing severity during the last t years.
Pain in Chest, Hoarseness, Roentgenogram Shows Tuberculosis of the Left Upper Lobe Sputum negative A few coarse rales. Temperature normal. N loss of weight.
First Arsphenamine Injection 3 dg Vomited. Secondary syphilid disappearing
Second Arsphenamine Injection 3 dg four days later No reaction.
Four days later pharyngitis, tonsillitis, palpable cervical glands, hacking cough audible rhonchi, nose running, temperature 101 F
Papular dermatitis on arms and legs, face swollen. *Patient had not received any mercury*
Put to Bed in Hospital Given 500 cc. Fischer solution (hypertonic saline and sodium carbonate) by rectum Temperature fell to normal in t elve hours.
Dermatitis Disappeared in Five Days. Probable ninth-day erythema.
Third Arsphenamine Injection 1 dg Given 500 cc. Fischer solution by proctoclysis in the following twenty-four hours. N complications.
Fourth and Fifth Arsphenamine Injections one and two eeks later 2 and 3 dg.; Fischer solution as before N complications.
Sixth and Seventh Arsphenamine Injections *3 dg 4 dg Through an oversight Fischer solution was not given after the sixth and seventh injections*
Dermatitis reappeared three day after the seventh injection ithout accompanying febrile or infectious symptoms, *following an attempt to begin inunctions* on the order of an inexperienced physician.
Typical Early Exfoliative Reaction Followed, controlled in ten days by:
Colloid bath, twenty minutes four times day
Potas imperialis by mouth.
Fischer solution by rectum.
Lassar paste (without salicylic acid) pplied to the skin between baths.
Tonsils showed evidence of chronic infection t this time

ing arsphenamine treatment are quit pardonable. On the other hand as Gjessing points out, early cases may be needlessly deprived of the benefits of an arsenical therapy a matter which was perhaps more serious in the mercurial days than under the present bismuth regimen. A certain number of arsenical erythemas must be regarded as inevitable and the possible instrumentality of an infection factor considered. Gjessing believes they are vascular infection-intoxication syndromes like the exanthemata. Fortunately the reaction is self-terminating and in the large majority of cases a change to a different type of drug permits the continuance of treatment.

The management of the acute process must be largely ymptomatic.

Salicylates sometimes seem to afford great relief but at other times are in effective. Alkalinization is useful. Great care should be exercised to protect the patient from chilling or the acquiring of an infection which may result at once in a rapid generalization of the dermatitis. Striking responses should not be too promptly attributed to the form of treatment employed.

The interrelation of ninth-day erythema with other forms of dermatitis occurring in the course of treatment which may assume something approach ing an exfoliative cast, is illustrated in Fig 197 Recurrences of ninth-day erythema with subsequent arsphenamine treatment but with diminishing severity have been recorded by Milian.

Treatment of Other Minor C taneous Complications.—The fixed exanthem, described by Naegeli in 1917 which takes the form of one or more urticarial plaques, reappearing at the same sit within few minutes to an hour or tw after injection and subsiding with residual pigmentation in the affected area or becoming lichenoid and sometimes eczematous, has been discussed in the American literature by Goldberger by Hazen, and by Chargin and Leifer (1940) and Mendelsohn (1940) is of unknow cause nd there is no known method of treatment. A spot of deepening pigmentation without preceding urticarial manifestations may develop When treat ment is discontinued the residue fades slowly Fixed eruptions produced by the arsenicals nd heavy metals are apparently identical in every respect with eruptions of similar type produced by other drugs.

Chargin and Leifer reported 60 in syphilitic patients 79 per cent occurring in the Negro, 19 per cent in the hite and 2 per cent in the yellow race.

Lesions ere most common on the face and were also observed over the entire body except on the scalp, palms and soles. The mucous membrane of the mouth was involved in t cases. Successful full-thickness autotransplants in three patients failed t react when the drug was readministered.

In spite of continued arsenotherapy no case of exfoliative dermatitis or any other type of arsenical dermatitis was observed in a patient having fixed eruptions. Since all trivalent arsenicals do not produce the fixed reactions with equal frequency it is possible t continue therapy uneventfully by change of arsenical. The various forms of herpes associated with arsphenamine and bismuth respond, following the discontinuance of the drug, t unfiltered roentgen-ray ultra violet exposure utohemotherapy and drying treatment ith simple calamine lotion. Ointments should be voided. Severe and extensive herpes zoster in these cases produces scarring characteristic of the condition. In one patient under treatment one of us (J H. S.) saw severe herpes zoster of the neck and right arm develop ith slight febrile reaction several days after an arsphenamine injection. T his astonishment, exactly fourteen days later this patient roommate developed chickenpox, a well-known association hich leads one to suspect that the herpetic omplication is an infectious incident as well as that the virus of the two conditions is identical.

Pigmentation and keratoses following the arsenicals cannot be materially affected by treat ment. When, ho ever the former occurs in association with dermatitic process it gradually fades. In severe cases of postarsphenamine dermatitis in brunettes it may be so deep as to suggest a mulatt tint. It is usually most abundant over the trunk but may involve the entire skin. A patient seen hen she had dermatitis and a mahogany-brown universal pigmentation, was rendered unrecognizable for us through recovery of her normal color hen seen six years later Argyria, of course is irremediable except as the local treatment described by Stillians and Laws can be pplied. Dohi has described postarsphenamine vitiligo or leukomelanoderma, ttributed to sympathetic nerve injury and Cannon and Karelitz have reported 3 cases of vitiligo following rsphenamine dermatitis.

The lichenoid or lichen planus-like arsphenamine eruptions respond as does lichen planus to unfiltered roentgen-ray irradiation, calcium and ultraviolet therapy and utohemotherapy

The pityriasis rosea-like exanthems and the flare-ups of dermatophytic processes observed under prolonged arsenical therapy and occasionall ith bismuth are believe exacerbations of mycotic eruptions and respond therapeutically t roentgen-ray irradiation, simple antipruritic lotions, weak sulphur ointments (1 t 2 per cent ith equal amounts of salicylic acid) and washes of 1 t 8000 potassium permanganate solution here they involve the flexures. A reduction in carbohydrat intake is essential here as in the exacerbations of seborrheic processes observed by Lee Harrison and Stokes. New types of arsenical cutaneous manifest tions have been recently reported which deserve mention vesicobullous dermatitis (Moir 1937); and reticular fibro-atrophoderma (Epstein, 1936) Benedek (1938) has collected group of cutaneous

disorders occasionally associated with arsenical and heavy-metal therapy (seborrheic dermatitis, pompholyx, pityriasis rosea and psoriasis vulgaris) under the title of "biotropic skin exanthems of known bacterial and hematogen endogenous origin" The various cutaneous and pigmentary disturbances from bismuth have been listed on page 200.

True Postarsenical Exfoliative Dermatitis—To this, the most serious of the cutaneous complications of treatment for syphilis, the term "late dermatitis" or "late exanthem" is often applied to distinguish it from the ninth-day erythema. Our observation would indicate that the individual who from the start shows a more marked cutaneous reactivity than the average, either by an outbreak of urticaria or ninth-day erythema is one likely to become the victim of true exfoliative dermatitis but this is by no means necessarily so As has been pointed out in the early part of this chapter the cutaneous explosion may be one of the unavoidable complications of even a properly conducted arsenical therapy and may appear early in the course of treatment,



Fig 198.— Fixed arsenical exanthem on the flexor surface of the forearm. This was the only lesion present. Originally urticarial, it recurred at first with each injection and finally became lichenified eczematous hyperpigmented plaque

though usually after the fifth to seventh injection. True exfoliative dermatitis, indistinguishable clinically from that produced by the arsenicals, may be produced by tryparsamide by mercury and by bismuth but is a comparative rarity Epstein (1937) believed that bismuth plays a major role in the production of dermatitis since he observed more cases in patients treated *with* the arsenical and heavy metal simultaneously This complication, it will be recalled, ranks second only to hemorrhagic encephalopathy as the most fatal of all unavoidable complications of a properly conducted arsphenamine therapy Its causal mechanism is considered on page 254

Prodromal Period and First Stage.—Postarsphenamine exfoliative dermatitis, dermatitis exfoliativa, or crustaceous dermatitis, tends in the majority of cases to follow a fairly definite course, with forewarnings constituting the first stage which, if recognized and treated may avert the attack. These prodromes with their general background are summarized in Fig 196 While one who is perfectly familiar with his ground may continue the treatment of

a patient under special precautions, after the appearance of one or another of these prodromes, the average physician invites trouble if he does so without advice. The second stage usually follows the repetition of the arsphenamine injection, which caused the prodrome, but may be delayed until after two or three injections.

Second Stage —Usually within twenty four hours after the injection which is to precipitate the severe attack, a general flush appears, most marked over the face and trunk with patches of dry or slightly oozing dermatitis, especially in the flexures and dependent portions of the body such as the feet and pretibial regions Itching is usually severe and the seriousness of the outlook may be to some extent gauged by the severity of this symptom by the degree of edema, and by the lividity or dusky bluish color of the involved skin. Figs 199 and 200 are typical of the severe attack. The general irritability of the



Fig 199 —Note the edema of the face early in the onset of serious arsphenamine dermatitis (Collection of Dr Joseph V Klauder)

patient is greatly increased and during the first three or four days it is almost impossible at times to secure his cooperation Chilling becomes very pronounced, due in part to the tremendous cooling effect of the cutaneous vasodilation. The patient's teeth may chatter in a room too warm for ordinary comfort. So continuous is this symptom that it may be difficult to recognize the really severe chills which often accompany the appearance or extension of the process and of coincident intercurrent infection which is often of the respiratory type. Fever may or may not be present (it appeared in two thirds of our cases, half just before and half during the dermatitis) but in the most severe cases usually reaching a peak of 102° to 105° F following a chill and then subsiding to the diurnal rise and fall of a septic temperature (see Fig 201)

It is at this stage as Moore and Keidel point out, that the blood picture is of value in detecting changes suggestive of early aplastic anemia and of marked irritation of the bone marrow

They found a striking increase in eosinophils, as high as 60 per cent in occasional cases, and in 14 of 16 observed patients there occurred an early leukopenia with decrease in polymorphonuclear neutrophils. Even an associated intercurrent infection, while producing a leukocytosis, was not sufficient to raise the proportion of neutrophils to the usual extent. Other cells of bone marrow origin appear in more severe cases, the large mononuclear transitional group even reaching the proportion of 30 per cent. Occasionally myelocytes and myeloblasts appear In extreme cases the bone marrow cells also disappear producing the picture of an aplastic anemia with extreme leukopenia and no signs of regeneration. These blood signs are all of some prognostic importance.

Third Stage —When the dermatitis becomes universal, the process settles down to a long course, seldom less than eight weeks and often as long as



Fig. 200.—Arsphenamine dermatitis. (Collection of Dr Joseph V Klauder)

twelve or more. The skin, at first deep red, edematous and oozing, becomes browner drier more leathery and scaling. The patient rapidly loses weight, and the skin, excoriated by scratching, hangs in folds. The hair thins, the nails usually are lost. Secondary inflammatory and infectious processes such as furuncles and mastitis develop Lymphadenopathy becomes general. The serous and mucous surfaces are often involved and obstinate conjunctivitis stomatitis, involvement of the auditory canals with furuncles and plugging from detritus add to the misery of the patient. Decubitus must be watched for in the emaciated and weak. Symptom from the throat and respiratory

tract are common, especially a tracheobronchitis. In patients who progress unfavorably a jaundiced tinge may appear but the liver is rarely palpable. There may be signs of nephrosis and a terminal exacerbation of infections, often a streptococcal pneumonia, may close the scene. Diarrhea is an obstinate feature of some cases and entirely absent in others.

In 1917 1918, 1919 and 1920 on the Mayo Clinic Service there were no cases with diarrhea, but in the 1922 epidemic all 5 cases of cutaneous reaction were accompanied by diarrhea, which in 2 cases was extremely serious and associated with such degree of ulceration in colon, sigmoid and rectum that one of the patients developed a rectovaginal fistula. From the bases of several ulcers an almost pure culture of streptococci was obtained. Examinations for other bacterial causes of colonic ulceration were negative. This, we take it, is only one of the evidences of the intervention of secondary septic infectious factors in the course, not to mention the etiology of exfoliative dermatitis occurring under treatment for syphilis. Michelson, for example observed streptococcus septicemia in fatal case of posttreatment exfoliative dermatitis.

A fatal outcome, when it develops, usually appears in the second stage of the dermatitis. In such cases, changes in the viscera indicative of acute arsenical poisoning are often found, as in the case reported by Latham. In other cases, acute fatal respiratory infections dominate the picture. In the later deaths in the third stage exhaustion, aplastic anemia, and septic complications combine to bring about the fatal issue.

Robinson and Roncheres have each reported gangrene of an extremity as a complication of exfoliative dermatitis in fatal cases, one with prodromal warning

An important consideration, leading in one case to a fatal termination, is that of the danger of tampering with focal infections during the course of the attack. In seven patients sharp flare-ups occurred in five following interference with a focus of infection the evidence tending to indicate that the action is indirect rather than direct. Tampering with foci of infection (tonsils, abscessed teeth) was responsible for death in one case which would have recovered without intervention and another patient was precipitated from a mild attack with prospective early recovery into the most severe and protracted case of Stokes Mayo Clinic series by dental extractions done on the ninth day of the dermatitis. Another case taught us the danger of opening a series of successive progressive infections during the attack of dermatitis. Subsequent cases (5) demonstrated, however the safety of removing foci of infection during rest periods and some weeks after the arsphenamine course Fig 201 is a graphic illustration furnished by the temperature chart of the dangerous effect of interfering with focal infections during the course of a dermatitis.

Fourth or Convalescent Stage —The signs that herald approaching convalescence are resumption of sweating which seems to be almost completely suspended, so far as visible perspiration goes, during the height of the attack improvement in appetite and spirits and decreasing irritability disappearance of chilling appearance of islands of paler skin, especially about the chest and over the knees decreasing scaling and thinner and larger flakes disappearance of edema and leathery thickening (lichenification) from the skin The face and extremities are usually the last to clear and the hair may completely fall out, before it and the nails come in again. For weeks after the patient is almost cleared up the feet will become purplish and edematous if the patient is about on them for several hours Itching is slow to disappear partly because the patient acquires the scratching habit, and maintains the

thickening and lichenification by rubbing and scratching more or less automatically rather than in response to definite itching. Pigmentation varying from a slight mottling to a deep bronzing, may persist for some time but ultimately clears up. Cannon and his associates (1942) have shown that poikiloderma like changes may follow arsenical dermatitis and result in permanent damage to the skin. At times the patient's complexion seems actually the better for the attack, but it is not uncommon for cutaneous irritability to persist for months and even years, expressing itself in patches of winter dermatitis on the legs or a seborrheic scaling in the scalp or on the chest. In such cases it is usually found that the patient was annoyed by dermatitis or had a seborrheic skin before the attack, and indeed that this was one of the factors predisposing him to his exfoliative reaction.

It cannot be overemphasized that patients who have once had the full fledged exfoliative dermatitic attack are the victims of a sensitivity to arsenicals particularly which will last in all probability for years, if not for life.

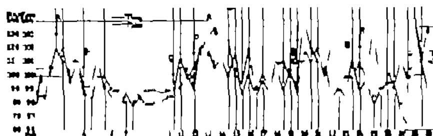


Fig 201.—Effect of interference with foci of infection on the course of postarsphenamine dermatitis: A, Fever accompanying extension of dermatitis after sixth arsphenamine injection. B fever subsiding, dermatitis improving; B–C dermatitis clearing up C, skin almost clear; tonsillectomy attempted patient refusing to permit completion of operation after tonsillar capsule was incised; febrile reaction D membranous tonsillitis developed, fever higher eruption previously almost gone, extending rapidly; E, eruption completely generalized, dusky livid hue, edematous, face swollen; E–F tonsillitis improving eruption somewhat less edematous and livid; F sharp chill, few râles at base of lungs, otherwise clear: skin exfoliating; G 8 teeth extracted, moderate reaction no change in skin H patient failing, scaling more pronounced steady decline until death five days later.

This is to be distinguished to some extent from the effects of the ninth-day erythema, but it cannot be too strongly emphasized that only under the most expert direction and with the greatest circumspection should any arsenical be exhibited to a patient who has once had a true exfoliative dermatitis.

The interplay of infection and allergy is well illustrated in many cases of exfoliative dermatitis One of our patients had seventeen relapses brought on by such episodes as nasorespiratory infection, relatively nontoxic drugs such as acetylsalicylic acid and so forth. Stokes and Kulchar' (1954) patients developed exacerbations after bismuth injection, exposure to goose feathers, and the development of cutaneous mycotic infection. The seriousness of this hypersensitivity is apparent from the fact that six years after an attack of exfoliative dermatitis which followed intramuscular injection of an arsenical, one patient was so extremely sensitive that single injection of mercury succinimide nearly provoked another attack, and the patient was likewise hypersensitive to iodide. It has been our experience that at least 50 per cent of patients who have had severe dermatitis must permanently abandon the intensive treatment of their infection. The unreliability of the patch-test for sensitivity should be recalled. It is also worth while recalling both the occasional response of exfoliative dermatitis to fever therapy and Simpson (1942) belief, and that of his coworkers, that exfoliative dermatitis is less frequent where fever therapy is employed in conjunction with chemotherapy While tryparsamide occasionally produces ex

foliative dermatitis, it is often a valuable alternate in cases of neurosyphilis. Serologic negativity may develop during an attack of exfoliative dermatitis, the basis for assumption regarding ecophylactic or protective effect. Epstein (1937) found these reversals to occur in about 60 per cent of his cases but Robinson (1913) believes that the rôle untoward reactions play in the cure or amelioration of the symptoms of syphilis or even in the reversing of a positive blood serologic reaction to negative if not without value, is, at best, negligible

The Prevention of Exfoliative Dermatitis.—No one who has had the opportunity to appreciate the misery expense and risk to the patient, or the strain on the physician, of a serious case of dermatitis will fail to realize that a gram of prevention here is worth many kilos of cure. Whenever a case of dermatitis occurs the physician should honestly and painstakingly search

Fig. 202.

THE ATTEMPT TO ABORT A DERMATITIS

1 All specific treatment instantly suspended
2 A complete blood count.
3. Sodium thiosulphate intravenously 0.5 0.75 1 Gm. on three successive or on alternate days for 3 injections may be tried. Vitamin C may be more effective
4 Additional well-recommended measures for alternative use
   (a) Bleeding (once) 200–400 cc. (Harrison)
   (b) Insulin, 5 to 10 units subcutaneously glucose solution 25 to 50 per cent 20 cc intravenously once or twice daily or on alternate days.
   (c) Calcium gluconate 10 cc of a 10 per cent solution intramuscularly or intravenously (very slowly) once daily or on alternate days, for 3 or 4 successive doses. (Karrenberg and Gerwig)
   (d) Quinine, 20–30 grains daily (Harrison)
   (e) Liver extract by mouth, intramuscularly (MacKee and Astrachan) or intravenously (Spethoff)
5 Removal of all surface irritants from the skin (mercurial ointment iodine etc)
6 Rest in bed, hospitalization preferred. Air-moistened room
7 *Avoid all chilling and keep respiratory infections* [illegible]*y*
8 A mild saline or alkaline laxative unless diarrheic Do not purge
9 High saline enema.
10 Fischer solution per rectum, 20-drop proctoclysis, [illegible] hours on, one hour off unless diarrheic.
11 Low carbohydrate, high protein and fat diet.
12 Starch bath if itching is severe followed by oily lotion (lime of olive oil and lime water equal parts) to be used only if no chilling or lividity
13 No tampering with focal infections.
14 No exposure to *erythema* doses of ultraviolet light

his record in the case and learn all that he can from it as to the prevention of such accidents. He will find however that even with the most meticulous precautions the complication is sometimes unavoidable Vigilant inquiry into the prodromal symptoms and the etiologic warnings contained in the patient's history as outlined in Fig 100, has none the less great preventive value

In view of the definite tendency for patients to separate themselves into reactors and nonreactors, those who show a persistent disposition to react whether with itching high nervous irritability repeated nitritoid reaction and repeated gastro-intestinal reactions should be regarded as potential dermatitis risks and treated with conservatism and under consultant advice if necessary No risks should be taken with pregnant women focal infection should not be tampered with if a cutaneous reaction has begun, local irritation

of a susceptible skin must be strictly avoided whether by innunctions or by applications of iodine especially and patch sensitization tests may sensitize the patient. (Beerman.)

The Attempt to Abort a Dermatitis.—A certain amount can be done to abort a threatened attack of dermatitis. Measures of known efficiency together with the most recent suggestions from the literature are included in Fig 202. We have often had the impression, however that "aborted dermatitis" especially cases in which sodium thiosulphate seems to have had miraculous effect, might, if allowed to run an uninterrupted course, have proved simply to be examples of ninth-day erythema. There is a steady march *from bad to worse*, an inevitability about the true attack of postarsphenamine exfoliative dermatitis which furnishes some of the really cheerless moments of syphilotherapeutic experience.

Cases which begin with a sharp chill, or chilly sensation and in which the dermatitis extends rapidly and early assumes a markedly edematous or oozing character with pronounced lividity can rarely be aborted and may in fact, be rapidly fatal. The patient who reaches his worst and begins to pass into the chronic phase by the end of a week or ten days will almost certainly make a good recovery In some patients the issue hangs in the balance for week after week and only the most skillful medical and nursing care brings them through. In settling down for the long siege, hospitalization is a great help, and special nursing practically indispensable, but the patient should not be exposed to the risks of moving to a hospital if avoidable once his condition is serious hence the desirability of hospitalization in the first place

Treatment of the Fully Developed Attack.—Some diversity of opinion exists with reference to the treatment particularly of the local phases of exfoliative dermatitis. In the acute phase the preventive measures of Fig 202 are in order As the case settles down to chronicity a choice between dry and wet methods of treatment, so to speak, may be made. Our experience opposes, largely on the score of the misery of the patient, the extended use of dry treatment and particularly the so-called "powder bath" if "wet" treatment can be had. Harrison, however recommends keeping the main surface of the skin dry with calamine lotion and calamine powder because the dryness antagonizes secondary septic infection. The bran bath is recommended by him when the scaling becomes too troublesome. An ointment of 2 per cent ichthyol in a bland base, such as rose ointment, is advised for the flexures, and may also be used on the face.

The Starch or Colloid Bath.—We have had better results from what might be called a wet method of treatment which consists in allowing the patient the free use though not the continuous immersion in a colloid or buffered bath prepared by suspending 1 to 2 pounds of powdered corn starch or laundry starch in the ordinary tubful of water In severe cases where hospitalization is possible, the continuous bathtub of full length with a temperature control valve (Fig. 203) placed in a suitable hydrotherapeutic unit is of much assistance. It is possible, however in a large bathtub in the home to carry out this treatment reasonably well, especially if the tub is so placed that it can be covered with rubber sheeting to keep the exposed parts of the patient from chilling

Certain details are of importance in the giving of the buffered bath. Oatmeal boiled to a porridge or thick gruel may be placed in a cheesecloth bag, this bag being then washed about in the water in preference to the use of

ordinary starch If there is much grease or detritus to remove one-half cupful of baking soda may be added to the tubful of water and dissolved in it before the patient enters the water In such a bath a dermatitis patient may soak for from fifteen minutes to one hour depending on his condition. He should not be overfatigued. O'Leary warns against the excessive use of the colloid bath as tending to produce waterlogging of the skin. While the patient is in the bath he may gently stroke himself clean or be stroked by the nurse using the flat of the hand without rubbing or scratching The water must not be hot but kept comfortably warm by adding hot water as the tub cools. Before putting the patient into the water the temperature should be tested with a bath thermometer 95° F being an optimum but a higher temperature sometimes being required on account of the tendency to chilling Debilitated pa

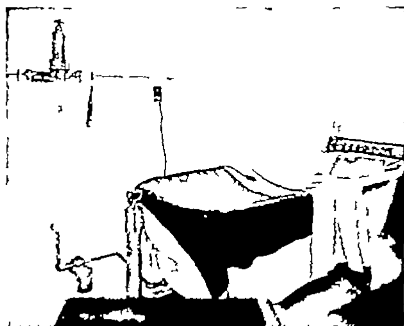


Fig 203.—Method of dressing the full-length tub for the colloid bath in treating exfoliative dermatitis.

tients should under no circumstances be left unattended. If the bath is warm an ice-cap on the head may be used but is seldom needed.

The moment the patient emerges from the bath he should be dried very rapidly by patting without rubbing and an oily preparation instantly applied If the patient is transported from one room to another or allowed to sit about for even a few minutes before the oily preparation is applied he is thereby made much worse. For this application rose ointment, plain or borated (2 to 5 per cent) or two parts olive oil, one part witch hazel water and one part lime water containing 2 drachms starch and 1 drachm glycerin to 6 or 8 ounces of the mixture, is satisfactory Antipruritics often irritate rather than help and even though the patient may demand them, should not be used.

Sterilization of hammock, sheets, towels, and cheesecloth bags when used is accomplished after washing by boiling in a solution of borax and washing soda, followed by thorough rinsing It is important to emphasize the necessity

for these precautions, for not only may the patient be severely infected by carelessness in this regard with the development of extensive furuncles and impetiginous lesions, but the attending nurses may acquire pyogenic infections of the fingers and arms. No bichloride, phenol, lysol, or other oily or irritant substance, however should be used in disinfection of the linen. The tub is cleansed by washing with lysol, followed by large amounts of hot water and then by vigorous scrubbing with a cleaning powder and rinsing with a bath spray and hot water There should be no odor of lysol about the tub when cleaning is completed. Systematic cleansing of this sort should be done daily soap and water being sufficient after the individual baths.

Additional Details.—Fig. 204 summarizes the detail involved in the management of a fully established case of dermatitis. If the case shows a distinct tendency to a pyogenic course, dry rather than wet management may be preferable. The fortification of general resistance by feeding vitamins (A and B) has at least theory to recommend it (halibut liver oil, yeast extracts) The daily administration of insulin and glucose throughout the course was the turning point in one of our patients and as in jaundice, helps to combat emaciation. Liver extract may also be used in accordance with the conceptions of Spiethoff and Milbradt and the experience of MacKee and Astrachan. Jenkins (1943) has tried histamine intradermally subcutaneously and intravenously from once in 1 to 3 days to three to four times a day (0 1 cc. of 1–1000 histamine dihydrochloride intramuscularly as the initial dose) He believes that the ideal results could be obtained by the simultaneous use of colloidal baths, histamine, ephedrine and phenobarbital. E Epstein in a controlled series found the method described in this text efficient. Local dermatophytic foci which may have predisposing significance (Stokes and Kulchar) may require conservative and consistent treatment.

Medicolegal Considerations.—It is well to bear in mind the medicolegal possibilities in a case of exfoliative dermatitis, and to make no unconsidered statements or permit others to make them.

Renal Reactions.—The mechanism and manifestations of renal reaction together with McFarland's conclusions from an extended experience with the behavior of the kidney under treatment for syphilis, are discussed in connection with the toxicology of the arsenicals and the heavy metals (pp. 200 218, 226 and 251) With the advent of bismuth there is a definite and gratifying reduction in renal reactivity to treatment. In combined treatment with moderation in dosage, reaction on the part of the kidney is almost negligible but should none the less be watched for by periodic urine examinations at intervals not greater than two weeks. Certain patients will tend to develop a treatment nephrosis. The susceptibility of the kidney to focal infection, giving rise to overloads on its excretory power is illustrated in Fig. 173 Wells and Sewell (1941) have shown that the combination of arsenical and heavy metal treatment and the hot weather (sweating) of the tropics lead to a toxic concentration of bismuth in the convoluted tubules—with resultant albuminuria but with normal kidney function.

Under routine treatment, therefore, one should not be too timid in the face of the occasional appearance of hyaline casts or a very slight albuminuria. There is a marked tendency toward spontaneous recovery from renal irritation even with the continuance of treatment, and attention to preventive detail usually does away with the necessity for any reduction in the intensity of treatment where intensity is desired or necessary The relative order of the

Fig 204

MANAGEMENT OF THE FULLY ESTABLISHED CASE OF DERMATITIS

1 Keep up nutrition by full soft diet and persuasion.
2. Keep sources of irritation and anxiety ay Systematic and sympathetic encouragement
3 Use every precaution t keep infections and carriers of infections, especially respiratory infections, ay
4 Nurses should wear rubber gloves, preferably elbow length, in handling patient and wash any exposed parts of their hands or forearms with tincture of green soap.
5 Keep bedding clean, changing daily
6 Give colloid bath two t *four times* day *ten to thirty minutes, according t strength* of patient. This is the best relief for itching Bathroom should be part of suit if possible and special care must be taken t avoid chilling or exposure Last bath at bedtime Optimum bath temperature 95° F but may have t be w rmer for chilly patients. Nurse must never leave patient alone in bath.
7 Grease the skin *at once* on drying (patting, not rubbing) after bath. Do this before leaving bathroom.
8 Lassar paste without salicylic acid, rose ointment, borated or not olive oil and lime water emulsion may be used t suit the individual case In some refractory cases goose grease is very acceptable later
9 Cover patient according t his wishes, t prevent chilling in bed.
10 Keep air in room warm (75° t 80° F) and moist.
11 Keep weight of bedding from feet by cradle and keep dependent parts elevated to control edema.
12. Discontinue Fischer solution and do not flood with fluids in the earl chronic phase or edema may recur
13. For the outbursts of oozing on face or extremities try bland et dressings (kept et, but not dripping) and bandages or mask.
14 Keep detritus removed by the bath, but trim skin tags from palms and soles ith scissors (don t allow patient to pull or tear)
15 Clipping the patient hair close makes cleaner scalp
16 Local infections (abscesses, furuncles, broken-dow lymph gland) must be tched for and promptly opened and drained.
17 Constipation in edematous patients ma be handled by catharsis, but in others is better dealt with by enemas, forced fluids and fruit juices, olive oil per rectum t be retained, and coarsening of the diet if tolerated.
18. For the conjunctivitis, zinc-boric solution, or if purulent, 10 per cent argyrol. Remove excess from lids to prevent local argyria.
19 For the lips, borated rose ointment. Keep the mouth clean and take out all removable dentures. If gingivitis and stomatitis are severe, treat as for mercurial stomatitis. Dental attention t gum pockets is very helpful.
20. Syringe out ears with arm boric solution occasionally and have excessive detritus removed instrumentally without trauma. Watch for furuncles.
21. W tch for decubitus and make every effort to prevent it, although it is not always preventable
22. If diarrhea develops, use hot saline irrigations, provided blood and pus are present or ulcers can be recognized proctoscopically
23. During convalescence reduce the scratching habit.
24. During convalescence increase the food intake and favor perspiration without chilling
25. I protracted cases, with persistence of patches, short general exposures t ultraviolet light (quartz lamp) and intramuscular injections of the patient own whole blood (10 cc. once weekly) may be helpful. Roentgen-ray unfiltered, in small doses under expert direction may be quite effective
26. The use of insulin and glucose, calcium, sodium thiosulphat vitamin C and of liver extract is given on pp. 363–368.

available drugs in irritation-producing qualities should be borne in mind, the iodides and arsenicals and tryparsamide being least irritating bismuth next and *mercury* the most troublesome of all. Temporary discontinuance of the

most irritating drug with mild alkalinization and a bland diet without alcohol tends to control irritation in a short time. The nephrosis tends to recover spontaneously within six months or a year on complete cessation of treatment. Patients with chronic nephritis are undoubtedly more reactive to treatment than normal persons but seem to make quite as satisfactory recoveries on suspension of treatment. The less irritating combinations, such as arsenical and bismuth should be used in cases of this kind Approximately one month is the proper time to allow for the urine to return to normal after stopping noncumulative heavy-metal treatment for syphilis. Renal hematuria is a serious sign of intolerance, and treatment should never be pushed this far Anuria, when it occurs as a complication of treatment is almost invariably the sequel of acid arsphenamine administration but may occur even after a single dose of a bismuth compound (thiobismol, Eitzen, 1937) Fischer's solution intravenously (see p 387) has provided thus far the only successful and indeed rational treatment. Decapsulation of the kidney can, of course, be considered but is rarely either feasible or practiced.

Pulmonary Reactions and Complications.—These have in part been considered under embolism (p 393) Iodide asthma an acute bronchial spasm with wheezing râles all over the chest, possibly due to pulmonary edema, occurs at times with intravenous sodium iodide administration and is at once relieved by 10 minims of 1 to 1000 epinephrine solution subcutaneously The possibility of acute edema of the larynx should be borne in mind, though we have never seen a case in thousands of injections. Precaution in not administering the drug to patients, whose tolerance of iodide by mouth has not been demonstrated, apparently eliminates this as a practical consideration. The pulmonary complications most frequently produced by the arsenicals are part of the mechanism of red blood cell agglutination with the formation of thrombi in nitritoid-like reactions already discussed. The symptoms are included in those of the nitritoid crisis and those of acid arsphenamine administration (pp. 391 400) Occasionally however the lung symptoms seem to be singled out for special prominence, and a sense of constriction in the chest, which rapidly passes off when the injection is stopped, or dyspnea, may express either changes in pulmonary blood pressure, transient flooding of the lung with minute erythrocytic emboli, or an actual arsphenamine asthma. All patients who have definite but not localizable pulmonary symptoms during injection should be kept in bed and under observation for two days to identify the possible bronchopneumonia which may ensue. Patients who cough severely *after any form of treatment should likewise be kept under observation for* from one to two days and inquiry made as to possible signs of embolus. These include pain in the side with a friction rub detectable on auscultation, or in the case of silent central emboli, rusty or blood tinged sputum. Arsphenamine asthma is a rare condition, usually accompanied by urticaria, coming on from twenty minutes to four or five hours after injection, and promptly relieved by epinephrine. It is apparently a true idiosyncrasy and argues a perhaps dangerous degree of sensitization. Great reduction in the next dose with the preliminary administration of ephedrine is the logical procedure.

The prevention of pulmonary accidents consists first in carefully checking the possibility of existing respiratory infection at the time of injection by questions, temperature report and physical signs second, in the use of neoarsphenamine or mapharsen if there is any intrinsic disease of the lung parenchyma, third, in the proper technic to avoid embolism, administration of in

Fig 201

MANAGEMENT OF THE FULLY ESTABLISHED CASE OF DERMATITIS

1 Keep up nutrition by full soft diet and persuasion
2 Keep sources of irritation and anxiety way Systematic and sympathetic encouragement
3 Use every precaution t keep infections and carriers of infections, especially respiratory infections, y
4 Nurses should wear rubber gloves, preferably elbow length, in handling patient, and wash any exposed parts of their hands or forearms with tincture of green soap.
5 Keep bedding clean, changing daily
6 Give colloid bath two t four times day ten to thirty minutes, according to strength of patient. This is the best relief for itching Bathroom should be part of suit if possible and special care must be taken t avoid chilling or exposure. Last bath t bedtime Optimum bath temperature 93 F but may have to be warmer for chilly patients. Nurse must never leave patient alone in bath.
7 Grease the skin *at once* on drying (patting, not rubbing) after bath. Do this before leaving bathroom.
8 Lassar paste without salicylic acid, rose ointment, borated or not, olive oil and lime water emulsion may be used t suit the individual case I some refractory cases goose grease is very acceptable later
9 Cover patient according t his wishes, to prevent chilling in bed.
10 Keep air in room warm (75° t 80° F) and moist.
11 Keep weight of bedding from feet by cradle and keep dependent parts elevated t control edema.
12 Discontinue Fischer solution and do not flood with fluid In the early chronic phase or edema may recur
13 For the outbursts of oozing on face or extremities try bland et dressings (kept et, but not dripping) and bandages or mask.
14 Keep detritus removed by the bath, but trim skin tags from palms and soles ith scissors (don t allow patient t pull or tear)
15 Clipping the patient hair close makes cleaner scalp
16 Local infections (abscesses, furuncles, broken-down lymph glands) must be watched for and promptly opened and drained.
17 Constipation in edematous patient may be handled by catharsis, but in others is better dealt with by enemas, forced fluids and fruit juices, olive oil per rectum t be retained, and coarsening of the diet if tolerated
18. For the conjunctivitis, zinc-boric solution, or if purulent, 10 per cent argyrol. Remove excess from lids t prevent local argyria.
19 For the lips, borated rose ointment Keep the mouth clean and take out all removable dentures. If gingivitis and stomatitis are severe treat for mercurial stomatitis. Dental ttention t gum pockets is very helpful.
20. Syringe out ears with arm boric solution occasionally and have excessive detritus removed instrumentally without trauma. Watch for furuncles.
21. Watch for decubitus and make every effort t prevent it, although it is not always preventable.
22. If diarrhea develops, use hot saline irrigations, provided blood and pus are present or ulcers can be recognized proctoscopically
23. During convalescence reduce the scratching habit.
24 During convalescence increase the food intake and f vor perspiration without chilling
25. In protracted cases, with persistence of patches, short general exposures t ultraviolet light (quartz lamp) and intramuscular injections of the patient own whole blood (10 cc. once weekly) may be helpful. Roentgen-ray unfiltered, in small doses under expert direction may be quite effective
26. The use of insulin and glucose, calcium, sodium thiosulphate vitamin C and of liver extract is given on pp. 385–389.

available drugs in irritation-producing qualities should be borne in mind, the iodides and arsenicals and tryparsamide being least irritating bismuth next, and mercury the most troublesome of all. Temporary discontinuance of the

tient to enormous doses of adrenalin was remarkable and several times we thought the tide turned in her favor. The dosage of epinephrine should be large enough to produce an effect; not less than 1 cc. of 1 to 1000 solution intravenously given slowly. It may also be given intramuscularly and is perhaps safer in this way. If there is response, larger doses may be given subcutaneously 1 or 2 cc. every two or three hours, the dose being reduced and interval being lengthened with the response. One fatal case showed definite response to doses as high as 5 cc. subcutaneously.

If seen very early during the stage of stupor or depression, before delirium or convulsions set in, the outlook is fairly good. In cases seen *in extremis* the technic of dehydrating the cortex, as in delirium tremens, by spinal drainage and the intravenous injection of 100 cc. of 10 per cent saline solution, may be tried. Undoubtedly a number of cases have passed as examples of hemorrhagic encephalopathy which have accompanying manifestations of hemorrhagic purpura with aplastic anemia and agranulocytosis. In these cases the outlook is very much worse and a blood count therefore should be taken in the effort to evaluate the situation. Lees reports obtaining blood from lumbar puncture at three different levels in one of his cases.

Differential Diagnosis.—The differential diagnosis of arsenical encephalopathy must be interpreted in the light of cerebral therapeutic shock (Herxheimer effect) and the various encephalitic manifestations involved in the differential diagnosis of neurosyphilis (p. 1018). Confusion with the convulsive seizures of general paresis, with status epilepticus, with syphilitic encephalitis, and with fulminating encephalitis of the epidemic type is possible. The administration of an arsenical injection within three or four days preceding the onset of the attack, is a suspicious circumstance and an epinephrine therapeutic test should be applied if the patient is not in convulsions. A spinal fluid examination should be made if there is no choked disk, and sodium thiosulphate may be given, though with what effect is, of course, uncertain. A previous history of seizures, due consideration of any apparent alcoholic factors in the case, apoplexy, fat embolism and so forth, must of course be had.

Therapeutic shock effects are particularly prone to manifest themselves in the nervous system when active lesions are present, and without doubt a proportion of cases of postarsphenamine myelitis, encephalitic syndromes following large doses of arsenical in patients with syphilitic encephalitis, cortical leptomeningitis, and diffuse vascular processes of a syphilitic type may confuse the picture. The cranial nerve injuries resulting from therapeutic shock in basilar meningeal and nuclear lesions when an arsenical has been administered suddenly in large dosage, are, of course, less suggestive of the encephalopathic picture. The majority of Herxheimer effects tend to appear after the first injection, so that their delay until the third, fourth or fifth injection argues rather for an arsphenamine complication.

Peripheral Neuritis.—Following prolonged series of the arsenicals and after massive dosage, prickling of the hands and feet with definite peripheral neuritic changes in occasional instances may be noted, but it is really remarkable how rare these effects are with the ordinary systems of therapy. Ehrlich early described the complication and Beeson observed a severe grade of peripheral neuritis with exfoliative dermatitis. Moore and Keidel have seen similar examples. We have known prickling of the hands and feet of neurocirculatory origin ("acroparesthesia") or from other causes of neuritis, to lead to considerable perplexity and a diminished intensity of treatment in early syphilis when the symptom was, so far as the arsenical therapy was concerned, without significance. The treatment in arsenical cases is that of all arsenical compli-

cations of arsphenamine administration In the pseudoreactions attention to focal infections, infra-red radiation, abstinence from alcohol and investigation of other drugs and causes of neuritis, should be made.

Peripheral neuritis in the massive dose arsenotherapy of syphilis by in travenous drip reached 35 per cent when neoarsphenamine was used but fell to 1 6 per cent with mapharsen. Part of the improvement was attributed to the employment of veins of the forearm instead of those of the cubital space with the resulting greater freedom of movement.

Hysterical seizures occasionally complicate the treatment of syphilis, as mentioned on page 411

Reactions Involving the Bones and Joints.—The arthritis and myalgia of mercurial and, to a much less extent, bismuth therapy and the occasional examples of arthritoid arsenical reaction with fever and erythema, are, we believe, attributable especially to the lighting-up of foci of infection in the body and not to the drug as such. Mercurial arthralgia particularly seems to have a definite association with bad oral hygiene and we cannot recall having seen it in patients under satisfactory prophylactic conditions. It may be neces sary to stop treatment in such cases until the focal infections are cleared up Salicylates give temporary relief Patients with multiple arthritis often cannot tolerate mercury at all by inunction, which is the particular form of admin istration most likely to give rise to arthralgic reactions, though they may be able to take it by mouth or intramuscularly Arthralgia may form part of the prodrome of infectious epidemic jaundice, together with urticaria (p 249) The jaundice usually begins about two weeks after the arthralgia. Bismuth grippe usually correctly identified only after it has been repeated once or twice, responds only to discontinuance of the drug

Reactions in Special Sense Organs.—Mercury and bismuth have no known effects on the special sense organs. The intravenous administration of mercury oxycyanide may be accompanied by a complaint from the patient that he smells bitter almonds and the odor during the intravenous administration of an arsenical has been mentioned A critical patient has assured one of us (J H. S) that colloidal mercury sulphide intravenously gives a definite sweetish taste.

The optic nerve, formerly regarded as a peculiarly vulnerable point (*cf* Skirball and Thurmon, 1935) in trivalent arsenical treatment is, we believe only occasionally affected by the drug *per se* (see p 264) DeSchweinitz has repeatedly emphasized his impression of the fibrous changes induced in the *eye under arsenical therapy of ocular conditions, but this is rather an aspect* of therapeutic paradox than of drug reaction as such. All treatment for syphilis has a disagreeable trick of hurrying into total blindness or total deafness patients with lesions of the second or eighth nerve of the atrophic type, but it is very difficult under these circumstances to feel assured that the effect is not that of therapeutic shock or paradox rather than a reaction to the drugs employed, as such We have, however so frequently seen this undesirable sequel to trivalent arsenical therapy in primary optic atrophy that we hesitate very much in the use of the drug, preferring rather to open treatment with bismuth which, at least so far as our experience goes, has shown no such effects. We have also seen ill effects follow a trivalent arsenical given to pa tients with nerve changes associated with high myopia in the absence of syphilis, so that we believe that the drug may be injurious to the optic nerve as such. In neurorecurrence involving the eye, mercury succinimide intra

muscularly four or five times a week with sodium iodide intravenously will produce a sufficiently rapid effect to make the use of the trivalent arsenicals unnecessary at least at the start. Injuries to the optic nerve produced by the pentavalent arsenicals (*e.g.* tryparsamide) are discussed on p 1045

Therapeutic shock, as has been stated, occurs in all acute processes in the eye when treatment for syphilis begins, even, paradoxically when there is no syphilis present, as in nonspecific therapy (see p 155) Hemorrhages into the vitreous may be precipitated in patients who have had them before, and a nonspecific uveitis may show a marked flare-up with subsequent improvement. A warning should be given relative to the importance of inquiry into ear symptoms before the first injection of a trivalent arsenical is given, particularly in early syphilis, for the effects of therapeutic shock in such cases are apt to be permanent and disastrous. The other cranial nerves have, in our experience shown no intrinsic drug reactions, whatever

CHAPTER X

TREATMENT PLANNING LATENT SYPHILIS AND OTHER COLLATERAL ASPECTS AND SPECIAL PROBLEMS

The treatment of individual manifestations of the disease is taken up in the appropriate chapters, but the whole subject needs to be pinned together by a treatment map such as is attempted in Fig 205 The rapid development of a "public health" point of view towards syphilis has emphasized for treatment purposes the division into infectious and noninfectious" stages. Treatment to noninfectiousness is a public health conception for which as yet, precise definition is impossible notwithstanding urgent demand. It can best be met, for mass action purposes, by considering the first four years of an infection of known duration as an over-all period of infectiousness, and by treating the disease within that period with maximum intensity for radical cure rather than for the mere abolition or prevention of infectiousness. The noninfectious period (the quotes signify the relative character of such a designation) covers the period from late latency to the end of degenerative manifestations or of life and is largely a period of individualization as distinguished from scheduled or system management. Late latency arbitrarily now regarded as beginning with the fourth year of known duration, is the last outpost of systematization and is dealt with in present practice by methods short of the radical but systematized and prolonged to secure all the advantages possible under the various conceptions of treatment effect, as a species of 'life insurance" protection for the individual against progression of his disease or transmission to others The overwhelming practical importance of this sandwich of early and late latency between the obviously infective and intensively treated early syphilis, and the relatively noninfective and individualistically treated late syphilis, is the really numerically important category of the mass treatment problem today

Many times in practice the management of latency seems to resolve itself into the question "how to treat when there is nothing to treat"—or more exactly how to treat when there is nothing but a positive serologic test. The American studies of latency from the clinical standpoint have performed the service of providing blanket coverage on a quasi-empirical basis, for a vast *terra incognita* in the life story of the disease which on the one hand satisfies public health requirements by a reasonable attack on the infectiousness problem and individual requirements by reasonable and probably maximum protection against the degenerative eventualities for the individual on the other hand. Such blanket coverage simplifies in a not undesirable fashion the thinking of the syphilologist, who for years had confronted with uncertainty the anxious and sometimes angry question, If he has nothing to treat but a blood test, why treat him?

With this map in hand then one can place his selection of treatment methods on a sound biological, public health and individual clinical basis.

The Conception of Latency in Syphilis.—One should review at this point the material of Chapter I on the biologic course of the disease, with particular

Fig 203

A TREATMENT MAP BASED ON THE NEW STAGE CHRONOLOGY OF ACQUIRED SYPHILIS

(Replacing Primary Secondary Tertiary Quaternary Time relations are approximate and overlapping)

	Stage	Chronology	Characteristic.	Treatment Aim.
Infectious Syphilis	1 Seronegative primary	First 1 to 2 weeks.	Phase of maximum curability	
	2. Seropositive primary	2nd wk. to 2nd mo.	Phase of undeveloped immunity and relapse tendency	
	3. Florid secondary	2nd to 6th month	Phase of median curability with persistent seropositive tendency	Treat with maximum intensity by system, for medical cure
	4. Late secondary and recurrent.	6th month to 3rd year inclusive	Phase of relapse—inadequate treatment, special resistance	
	5 Early latent.	2nd to 4th y incl.	No manifestations.	
	6. Late latent.	4th year onward	Phase of benignity no manifestations, seroresistance, congenital transmission, progression.	Treat by special standard for "life insurance" to stop progression or transmission.
"Non-infectious" Syphilis	7 Late syphilis of special structures			
	a. Precocious tertiarism.	Harks back to (2), (3), (4)	Result of inadequate treatment, low resistance	
	b. Late destructive recurrences.	Harks back to (4).	Mostly skin, bones.	
	c. Special sense organs, especially eye.			Treat by individual methods of graded but adequate intensity to repair damage stop progression, "cure" if possible.
	d Inflammatory skeletal syphilis.		Gummas, osteitis, osteomyelitis, etc.	
	e. Early cardiovascular syphilis.	4th year onward.	Early aortic change peripheral accidents.	
	f. Asymptomatic and early neurosyphilis, preponderantly meningovascular	1st month onward.	Abnormal spinal fluid, slight clinical changes.	
	g. Late cardiovascular syphilis.	10th year onward.	Advanced aortic valvular and aneurysmal disease.	Treat individually avoiding shock and paradox, for symptomatic relief, and to stop progression.
	h. Late neurosyphilis, preponderantly parenchymatous and degenerative.	4th year onward.	Tabes, paresis.	

CONGENITAL SYPHILIS FOLLOWS THE CHRONOLOGY FROM (3) WITH EMPHASIS ON (7)

emphasis from the clinical side on the discussion of the Bruusgaard statistics and other evidence of a strong tendency to years of asymptomatic course terminating in trifling benign manifestations mere landmarks such as persistently positive serologic tests, or microscopic evidence of the disease recognized only at autopsy after death from other "normal" causes

Three tendencies have marked the development of thinking within the past decade on the essential nature of latency The first of these is the extension of the serologic test on the blood to the well individual, in contrast with the sick. This might reasonably be expected to expand immensely the inert asymptomatic, nonprogressive syphilis recognized, as well as that portion of such latency as was headed for future disaster From what we now know of the behavior of the disease, we reasonably expect the expansion in the direction of innocuous latency to be more rapid than in the direction of potentially disastrous outcomes of latency

A good cross-section of the latency problem in current syphilologic practice is afforded by the statistics of the University of Pennsylvania Hospital clinic for the five years, January 1938 to January 1943 inclusive. Of 1813 syphilitic admissions, 61 per cent were diagnosed as latent syphilis. Of the 1114 cases, 15.8 per cent were diagnosed as early latent syphilis, and 84.2 per cent as late latent syphilis. Of the 176 early latent cases, 21 per cent were diagnosed as seronegative latency and 79 per cent as seropositive latency Of the 938 late latent cases, 14 per cent were diagnosed as seronegative and 86 per cent as seropositive latency

It is therefore reasonable to suppose as far as treatment is concerned, that the amount of recognized latency really requiring treatment, as distinguished from theoretically will decrease in proportion to the whole, rather than increase. The question of whether or not to treat latency at all, and how much treatment to give it, may therefore be expected to sustain considerable readjustment in the coming decade The second tendency is for writers to become over-analytical, and to develop an esoteric terminology for a relatively simple matter The subdivision of latency into types always carries this danger with it. Where there is nothing to describe, the effort to describe it in many words may be confusing We have not therefore, at this point, introduced into our discussion of latency the subdivisions of Moore (1932, 1933 1937–9) including clinical, serologic and pathologic types. Whatever else it may be, latency must be syphilis, demonstrable as such by evidence acceptable to the critical mind In the direction of latency with negative blood serologic tests, it collides with the growing conceptions of cure. In the opposite direction *it collides with the inescapable fact that even death from syphilis may ensue* upon a state of complete serologic negativeness. Seronegative latency may be identified by history on the evidence of credible authority that the disease has existed, even though it is now silent by inescapable evidence that it has existed in the form of symptomatic or physical scars. Seropositive latency collides at the one extreme with the biologic false positive test reaction and our ignorance of the "reagin" mechanism at the other extreme with the undoubted existence over periods of years, even to the termination of life in its normal course if a totally irreversible serologic reaction unaccompanied by any symptomatic or physical sign of the disease.

It becomes apparent then, that latency is practically more a matter of what it may become, than of what it actually is, for as it is it is nothing so far as our clinical criteria of significant change are concerned. Latency is syphilis identified by some controllable and trustworthy evidence that the infection

is present but unaccompanied by any evidence that it is clinically active. Monosymptomatic seropositive latency is the largest single category in the group. It has been over-expanded to an unknown but probably large degree in the past, and one causing much concern in the present by the biologic false positive serologic test which has undoubtedly swelled the roll of latency by many persons who do not have syphilis at all but who on serologic findings have been diagnosed and treated. Until the syphilitic reagin can be tagged as to specificity by the identification of its precise nature and tests for its identity latent syphilis remains a parlous diagnosis capable of reflecting discredit on technical medicine and, in theory at least, injury upon the patient.

The process of establishing the existence of latency is outlined in Fig 206 To every individual investigated for the presence of latent syphilis, the fine-tooth comb of anamnestic and physical examination must be scrupulously critically and completely applied Broadly speaking the more detailed the examination, and the more expertly performed the better the likelihood that

Fig 206

TO ESTABLISH THE EXISTENCE OF LATENCY

1 Establishing latent syphilis as diagnosis includes
   ( ) Proving the presence of the disease
   (b) Excluding every clinical evidence of its activity except the serologic tests on the blood.
2. Proving the presence of syphilis includes
   ( ) The complete physical examination and history Turn t Figs. 12 and 13, Chapter II, keeping in mind the causes of biologic false positive tests, Fig 33.
   (b) Checking the validity of the positive blood serologic test. Turn t p. 63.
   ( ) Competent special examinations of the yes, the bones, the cardiovascular stripe (fluoroscopy etc.), the stigmatized structures (bones, teeth) for evidence of congenital or acquired syphilis, as indicated.
   (d) Examination of the spinal fluid.
   ( ) Study and examination of family and sexual contacts
3. If ( ) and ( ) under 2 show active syphilitic processes, the case is not latent.
4 Excluding all clinical evidence of activity means ( ) and (d) negative

THE BLUNDER OF THE (QUARTER) CENTURY—DIAGNOSING LATENCY WITHOUT A CONFIRMED BLOOD AND A SPINAL FLUID EXAMINATION

the disease will be identified, and more than one evidence of its presence be forthcoming If the evidence is other than a pathognomonic scar or such a fact as the giving birth to a syphilitic child, which in present knowledge automatically establishes the existence of syphilis in the mother the question arises as to whether the infection should be designated as active rather than latent. A positive blood serologic test of syphilitic origin is still accepted as presumptive evidence of the existence of a live" infection. It remains to be seen whether it persists after the extinction of the last spirochete—a question perhaps resolvable by ultraintensive therapy followed by quantitative serologic tests and with autopsy control. When we speak, therefore, of the positive serologic test in prolonged asymptomatic latency as a scar of the disease we are taking inferential license for the comfort of the patient and in recognition of the Bruusgaard and other experiential evidence of benignity When, in the examination of latent syphilis, detected by a positive blood serologic test, an abnormal spinal fluid is unearthed, the diagnosis of latency is dropped,

and that of asymptomatic neurosyphilis substituted because experience of the benignity and nonprogressiveness of a neurosyphilis defined by an abnormal spinal fluid pattern is small and the evidence in favor of activity and grave progressive tendency overwhelmingly the greater Nonetheless it is not inconceivable that time will justify the position that there is a true latency with at least a positive serologic test on the spinal fluid, and perhaps abnormal protein levels and an abnormal colloidal test. The presence of vascularization in the cornea on slitlamp examination the identification of proliferative change, the sequel of old periostitis and a number of other residues of syphilis identifiable in the examinations outlined under Fig 206 carry with them this inevitable clinical uncertainty as to whether they are the scars of an old or dead process, or the wave traces on the bodily shore of what may prove ultimately to be an inevitably though intermittently advancing tide of syphilitic complications and sequelae.

Since the decision as to what shall constitute latency and what its ultimate meaning or destination may be carries these inevitable elements of uncertainty the treatment policy both from the public health and the individual standpoints must inevitably lean towards treatment, and not away from it. The decision not to treat in the presence of evidence that a syphilitic infection has existed, even though now quiescent, is a critical one and not to be lightly undertaken. The inclination must be to treat the infection if

1 The latency is of undetermined, but presumably relatively short duration
2. The individual is young or has a reasonably long life expectancy
3 There has been evidence of a trend towards infectious recurrence.
4 The patient is a woman, who, regardless of social status, may still become pregnant, thus endangering the child.

On the first of these considerations, it may be assumed for arbitrary mass classification purposes, that most syphilis is acquired before the age of thirty or even twenty-five. An infection identified at age thirty two may be assumed depending somewhat on the life history and make-up of the individual, to be an early rather than a late latency since the tolerance of treatment at this age is good, the decision will lean towards intensive curative measures, perhaps, rather than towards a system for "life insurance" In a patient of fifty it may be assumed that the latency is of at least twenty years duration the life expectancy at best not more than twenty years infectiousness over with the likelihood of progression reduced to lowest terms, and the necessity for intensive measures therefore nil and for routine life insurance" therapy minimal if not actually nonexistent. On the other hand, in an infection acquired at age sixty latency at age sixty-five has more of the qualities of early than of late latency from the public health if not the individual standpoint, and though the life expectancy may be short, the danger of transmission may be considerable Treatment, accordingly leans towards maximum intensity rather than routine "life insurance." At this point one of Moore s tabulations, essentially an astute guess is of great suggestive value.

Moore further estimates, to quote his own words, "In those infected less than five years, the probable outcome without treatment may be assumed to be essentially the same as for early syphilis itself i.e 25 per cent spontaneous cure, 25 per cent continued latency 25 per cent probability of late allergic gummatous lesions 25 per cent risk of cardiovascular or neurosyphilis.

Moore has pointed out the importance of race and sex in the prognosis of latency rating Negroes as much more prone to develop late lesions, especially of the cardiovascular type, than whites and women notably less likely to develop manifestations of the disease than men. The Negro woman has a particularly benign and prolonged latency which however must be matched against her established greater tendency to infectious lesions early in the course of the disease. It may be quite safe according to Moore, to withhold treatment completely from a woman past the menopause, while to a man of comparable age it should be given. Moore well emphasizes the principle reiterated in this discussion, that generalizations about latency have mass rather than individual application.

In the past twenty-five years, the pendulum has accomplished a complete back-and-forth swing from an original disposition on the part of older physicians to minimize latency and for the patients gladly to accept the policy of noninterference, through the day of the younger generation of physicians who reacted to the positive serologic test as a bull to a red rag In the middle

Fig 207

PROGNOSIS OF LATENT SYPHILIS (UNTREATED)

Duration of Infection	Probable Percentage of Spontaneous "Cure or Continued Latency	Probable Percentage of Future Lesions
0–5 years	60	40
5–10 years	70	30
10–20 years	80	20
20–30 years	85–90	10–15
30 years	90–95	5–10

(J E. Moore, personal communication)

ten years, the patient in his turn alarmed by gradually spreading knowledge of the prevalence and seriousness of the disease, accepted treatment with alacrity and pursued it often with insistence. The combined effect was expressed in a *furor therapeutica* which justifies the aphorism of Fig. 208 to the effect that most latent syphilis today is underexamined and overtreated. Now the pendulum is again swinging towards conservatism the disposition is towards moderate rather than maximal treatment, and the punishment of latency for being caught with a positive blood test is being reduced and in more cases, remitted altogether

Active Process *versus* Residuum.—The decision as to whether one is dealing with an active syphilitic process or a residuum is sometimes extremely difficult and critically important because if the structure involved is vital the process may be more advanced than clinical signs indicate, more subject to therapeutic shock and paradox which alter the mode of approach. Here again, the wiser policy is to lean towards the diagnosis of active infection rather than the diagnosis of latency This consideration has probably led to such anomalies in diagnostic terminology as "latent cardiovascular " "latent

neurosyphilis" and so forth. There is of course no object in treating a patient for a scar such as a fixed pupil or an absent knee-jerk which cannot as a rule be affected in any way On the other hand, the mixture of scar and active inflammatory process which a case often represents can be materially benefited—the relief being proportional to the amount of active inflammation. For example, corneal vascularization in an interstitial keratitis offers little outlook for improvement but if any evidence, even the slightest, of activity in the form of punctate infiltrates can be found the response to treatment may be surprising In such a case the decision to treat the patient for active syphilis and so to diagnose it is wiser than to accept latency as established and withhold treatment for conservative reasons or inertia. Such situations in general are saved by the principle of leaning toward treatment, and treatment for "life insurance" previously enunciated In such cases, the decision to treat the patient for syphilis may rest entirely with a specialist in another field, as for example early manifestations of involvement of the aorta, short of symptomatically demonstrable early aortitis. This field in particular is critically important, and the *shortcomings of clinical recognition of aortic syphilis* have been amply set forth in the classical work of Moore Danglade and Reisinger in their comparison of clinical and necropsy observations on 105 patients Few diagnoses are more risky than that of latent syphilis in the presence of even the slightest recognizable evidence, clinical roentgenologic or other of abnormality of the cardiovascular mechanism with a fair presumption of the presence of syphilis. (This work is subsequently referred to in the chapter on cardiovascular syphilis.) In some cases, such as retrobulbar neuritis, recent eighth nerve deafness, Bárány syndromes in syphilitic patients, persistent subjective symptoms in neurosyphilis such as lightning pains and headaches, and even constitutional subnormality without localizing signs, it may be desirable to treat what would otherwise be called a completely latent or "burnt out" infection because of the possibility of benefit. This is not a therapeutic test to establish the existence of syphilis for the diagnosis may be perfectly apparent, but a test of the treatability of what would otherwise be called a latent or inactive infection. In all such cases, treatment once begun must be carried to completion in accordance with a reasonable modern standard.

The Treatment of Latency —Because of its close relation in present-day practice to the more intensive treatment of early and potentially infectious syphilis, the modern optimum system for the treatment of latency is discussed in Chapter XIV

Irrespective of the treatment itself four principles deserve emphasis here. First, it is unjustifiable to disturb immunity relations in a patient with a latent *infection unless treatment can and will be carried far enough to block* the likelihood of induced allergy particularly from the arsenicals, and reactivation of the infection by short courses, inadequately followed through Milian has been particularly emphatic in his objection to undertreatment, not however particularly in the field of latency to which nonetheless, many of his conclusions might easily be applied. Treatment of the latent patient by opportunistic management following surgical operation in which the syphilis casually recognized as a possible factor in the situation receives a modicum of unwise attention in the form of a few "shots" is particularly undesirable. From what we know of the behavior of the arsenicals, this is a method of stimulating rather than retarding the course of the infection in an unknown proportion of patients.

A second principle applicable to the treatment of latency is that of beginning treatment with a heavy metal rather than an arsenical. With mapharsen this objection is perhaps less significant, but it is nonetheless a wise concession to shortcomings in examination and in the appraisal of the activity of the process, to begin by "preparation" methods with a heavy metal appropriate to one's estimate of the weakest spot in the situation rather than to run the risk of therapeutic shock, remote though it may seem.

A third principle is to close treatment with a heavy metal rather than an arsenical in order to leave an absorption depot and prolong effects for the protection of immunity. In fact, it has been in latency that the principle of

Fig. 208.

SOME DON'TS FOR LATENCY

1. Don't call patient latent on the basis of casual inspection and arm-chair examination. Distinguish between actual and spurious latency.
2. Don't decide the latency of case without examination of the spinal fluid and the cardiovascular mechanism.
3. Don't neglect any opportunity to secure base-line examination of the patient with syphilis early in his infection. A negative examination may be as valuable as positive in latent and later years.
4. Don't lose sight of seronegative latency especially in women who have had or may have children.
5. Don't forget that the prenatally infected child is presumptive proof of its mother's latent infection. Examine children as well as parents.
6. Don't lightly authorize pregnancy in latent syphilitic women. Insist on treatment.
7. Don't pound latency indiscriminately with intensive treatment. Consider the objective, the age, and time factors.
8. Don't begin the treatment of latency with an arsenical. Prefer bismuth, or even mercury and iodide.
9. Don't disturb immunity relations in latency with few shots of anything, especially an arsenical. If once begun for good cause follow through and end with heavy metal.
10. Don't treat even the most eligible and willing latent patient beyond the standard for early syphilis (p. 630). Refuse to be party to robbery or aggravated assault and battery even in the name of positive serologic reaction and the patient's demand for pure blood.
11. Don't casually withhold treatment because the patient "looks well"; realize the seriousness of putting him purely on his defence mechanism.
12. Don't dismiss the latent patient as "cured." Reexamination at intervals will, with expert assistance, compensate most errors of judgment in time.

MOST LATENCY IN SYPHILIS TODAY IS UNDEREXAMINED AND OVERTREATED

periodically renewing the patient's supply of heavy metal, so to speak, has led to the "course-a year" principle, indefinitely prolonged, which has been slowly gaining in popularity since the publication of the Cooperative Clinical Group reports.

A fourth principle and, in some respects, the one most abused in present day practice, opposes the year-in year-out pounding of the seropositive latent case in response to the physician's serology-bound conception that he ought to be doing something as long as the blood test is positive, or the patient's neurotic self-condemnatory feeling that he will never stop treatment until his blood is pure. The adoption of a reasonable standard of protective treat

ment will perhaps do away in time with the excesses and abuses which now constitute so serious a drain on treatment resources without corresponding advantage to the patient.

Observation Throughout Life.—Our present conception certainly permits us to believe that latency may eventuate in spontaneous cure. On the other hand this is wishful thinking rather than a fact established by autopsy protocols and experimental evidence Accordingly it is inadvisable to give the treated latent patient the impression that he will be cured in the strict sense by our intervention and he should be impressed with the necessity for *maintaining a reasonable schedule of periodic reexamination all facts dis-*

Fig 209

WHAT TO SAY TO THE SEROLOGIC "PICK-UP"
(The Patient Identified by Routine or "Survey" or Premarital and Prenatal Blood Tests)

1 Think before you speak. Remember a single positive blood test is not a diagnosis; recall the possibilities of biologic false positives, repeat the test; then recall that it does not define or describe the type of syphilis. That must next be delineated Do a complete physical examination get a complete history
2 Be tactful and cautious. Gauge the mental and emotional status of your patient, gain his or her confidence explain the importance of proving or disproving the presence of the disease your approach should be as follows—

3 Cheer up! It may not be true Even if we do find you have the disease it might be worse Let us approach the problem together
4 Did you ever have a blood test before? When. Who took the test? Was it positive? Was it repeated? What did you do about it? Any treatment? Who gave it? About how much?
5 What diseases and infections have you had recently? Vaccinated sore throats, colds, etc ? Try to give the dates.
6. Have you actually to your knowledge had syphilis, been told you had it; been treated for it? Give us the facts for your own sake
7 Tell me about your family—father mother brothers, sisters your sex contact and habits.
8 Are you, or have you been, married? Contemplating marriage? Have a sex partner? If you contemplate marriage or other grave commitments, better postpone them for three months. Expose no one sexually or by intimate contact until the situation is clarified If you are married, we should test your wife and children, but only after we have raised a strong presumption that you have the disease
9 Do not start treatment in a panic for a disease which you may not have Have a competent investigation made and see where you stand
10 Avoid pregnancy or the likelihood of becoming pregnant until the question of your having the disease is answered. If you are pregnant, a prompt decision on this matter is imperative lacking which it may even be advisable to assume the presence of the disease and undergo treatment to protect the baby Do not procure an abortion.

closed throughout life This need not of necessity include reexamination of the spinal fluid which according to Cooperative Clinical Group investigation once negative, is likely to remain negative On the other hand, a latency reduced to the seronegative state by treatment needs serologic as well as clinical controls. If especially in an early latency a blood test is negative for as long as a year and then becomes definitely and repeatedly positive (to be distinguished from the up-and-down or see-saw of partial positives and negatives in some latent cases after treatment) a reexamination of the spinal fluid is indicated. In the light of what we now know of the progression of cardiovascular syphilis under the mask of serologic negativeness or the see-saw

fluctuation of negatives and partial positives, it is also essential to have a fluoroscopy of the cardiovascular stripe an electrocardiogram, and if possible, a skilled interpretation of the physical signs and symptoms of early cardiovascular disease, at least once in five years, during latency no matter how prolonged. It is a fair presumption that if nothing has appeared by the end of the first decade, nothing is likely to appear but it is by no means a safe assumption, where the greatest safety for the individual is desired. In all advice to latent patients under observation, the anamnestic inquiry and the physical examination should be as conscientiously performed as the original study the interval between such checks should not exceed three and perhaps even two years and some thought regarding the contributory effects of over strain and trauma in the patient s life should accompany the advice covering the interval to the next examination.

The Cooperative Clinical Group studies of the treatment of latent syphilis, while they do definitely support the thesis of leaning towards treatment rather than away from it, contain some rather surprising evidences that once late latency at least is established, it makes little difference what one does, the patient comes out all right. For example, the satisfactory results under a wide range of treatment, from little or nothing to much arsphenamine range close around 50 per cent, but leap to 95 per cent when little or no arsphenamine but much heavy metal was employed (small number of cases) The result in one of the cooperating clinics on patients treated with heavy metal for years, without any arsenical treatment, tended to indicate that the prolonged use of heavy metal after all is what gives ultimate satisfactory results in latency This raises directly the question of treatment throughout life which was informally the vogue in the days of mercury and iodide by mouth, sustained a set-back as the toxicity of the more intensive methods and the newer drugs became apparent, and is now in process of revival as a treatment concept with the demonstration of the relative innocuousness of bismuth. Therapeutic "pecking" with "a course a year may now be accepted as good practice and insofar as it gives both patient and physician a feeling of assurance and prevents the development of syphilophobia and neurosis under the "observation throughout life concept, it may be conceived as desirable practice. In the relatively long heavy metal sessions of the standard treatment of latency subsequently discussed, a tapering off in the form of a course a year for from three to five years, following the completion of the formal requirement, is not unreasonable, though we are not as yet ready to subscribe to the conception of a course a year" even of bismuth, throughout life.

Latent Syphilis and Pregnancy.—While the treatment of syphilis in pregnancy is more fully discussed on page 1148, it is proper here to point out that apparently latent syphilis is one of the most important and most serious sources of the prenatal infection of the child For that reason, all considerations concerning the women with latent syphilis tend to revolve about its relation to her childbearing age and capacity For the diagnosis of syphilis in the woman an examination of her children is often necessary as has been said. The syphilitic child is *ipso facto* evidence that its mother had the disease, and the presumption is that, if living she still has it. Women with latent syphilis who may become the mothers of children should be treated in anticipation of conception and during pregnancy with all the judgment but nonetheless with all the determination that the occasion may require. The studies of the Cooperative Clinical Group, with Moore as spokesman show unmistakably how

serious is the toll in injured and infected children that the latent infection in the woman takes. Treatment of the latent syphilitic mother during pregnancy regardless of the amount, increases fourfold from 16 to 65 per cent the chance of obtaining a normal baby

Active Benign Syphilis.—The management of benign but active *syphilis* is a step beyond the problem of latency for the obligation to treat the patient is more apparent. At the same time it is important to keep fundamentals in mind, and to avoid exchanging a benign lesion and an effectively working defence mechanism, for some serious loss of resistance and a flare-up of dangerous proportions. An examination of spinal fluid and cardiovascular system is in order especially in those under sixty The patient who presents only trivial lesions of the bones and skin four or five decades after infection, should not be pounded with the heavy artillery of modern treatment. In such cases it is even distinctly risky to use the arsenicals because of their allergy-producing properties. Resort may well be had in such cases to mercury or bismuth (Sobisminol) by mouth and iodide to slightly more intensive mercurialization or to intramuscular bismuth therapy (iodobismitol) instead. On the other hand, in earlier life the appearance of even benign lesions must be the signal for thoroughgoing treatment and prolonged observation.

THE FIXED POSITIVE SEROLOGICAL TEST IN TREATMENT

Fixed positiveness or serological fastness has been discussed from the diagnostic standpoint on page 100 Chapter IV The essence of a fixed positive test is its failure to become negative under prolonged intensive treatment Few outcomes *more completely discourage and puzzle the conscientious* and well-meaning physician and patient.

Classification of Serological Fastness.—Four types of serological or reagin fastness or fixed positive Wassermann tests can be recognized in clinical practice, as follows

1 Fixed positive sequels of inadequate or ineffective treatment of early syphilis.

2. Fixed positives representing visceral, vascular and nervous system disease.

3 Reactivation of weak or partial positives which become strongly and irreversibly positive after treatment.

4 Monosymptomatic irreversible positive serological tests, in the absence of all other signs of the disease usually occurring in late latency and usually devoid of serious prognostic significance

By way of general discussion of these four types, it must be pointed out that the positiveness and the persistence of a serological test is a function of the technic of serological procedure employed. With the introduction of increasingly sensitive and yet specific modifications it is possible that a large proportion of established syphilis regardless of treatment, can be found to carry a partial or even a strong positive by the sensitive procedure, throughout the larger part of life. It is apparent, therefore that serological fastness is a relative matter at best.

Attention has also been called in the literature t the fact that ven strongly positive serological tests, if carried out quantitatively t the proper point, show variation and definit im provement under treatment when such improvement does not ppear in the routine test as performed for diagnosis (Coleman, Casselman, and Patterson) Quantitative procedure also shows many persistent seropositives of relatively low titer Spontaneous nd inexplicable vari

tions in the serological tests of patients with supposedly fixed positive Wassermann reactions observed over a period of years have been recorded by Gougerot and Peyre who found several such cases completely negative to repeated testings over periods of months in the course of many years of what would otherwise have appeared to be absolute serological resistance. Some of the up-and-down see-saw of fixed positive serology is of technical origin.

Fig. 210

SOME FUNDAMENTAL FACTS REGARDING SERORESISTANCE OR FASTNESS FROM THE TREATMENT STANDPOINT

1. **Seroresistance has increased** with the increasing sensitiveness of tests (Eagle 1937—100 per cent serofast in 1937 would have been 70 per cent in 1920, 28 per cent in 1907).
2. **The normal course of the reagin curve** is slowly downward with undulations and an ultimate low titer. The longer latency is observed the less seroresistant residue remains.
3. **Not knowing what reagin is,** we do not know outright when to treat its presence as active disease, when a scar.
4. In general, then, serologic fastness is a **sheaf of laboratory reports** (O'Leary) subject to therapeutic interpretation in terms of time and other findings.
5. In early syphilis it is serious, presaging relapse, infectious and otherwise, cardiovascular and neurosyphilis. In late syphilis, once visceral, cardiovascular and neurosyphilis are eliminated, it is not.
6. **The proportion of absolute seroresistance** to effective treatment (two years or more of combined therapy) rises from 11 per cent in early syphilis to 75 per cent in paresis. Latent syphilis rates 33 per cent, meningovascular 46 per cent, late cutaneous 50 per cent, cardiovascular 50 per cent, late visceral, late osseous, late congenital, 60 to 70 per cent (Moore and Padget 1936, and Cooperative Clinical Group)

The residue of seroresistance varies with the type of treatment employed in early syphilis; continuous 11 per cent, intermittent 37 per cent, irregular 68 per cent (Cooperative Clinical Group). Continuous treatment in early syphilis is the great preventive.

8. **Shortening or premature stopping** of the early treatment courses (first four to seven months of treatment) and especially of the arsenical, predisposes to fastness.
9. In the first year neoarsphenamine is less effective than 606, mapharsen not yet evaluated.
10. **Arsenical bismuth therapy** is superior to arsenical-mercury.
11. **Overmassive** or insufficient treatment, after the first year predisposes to seroresistance. Continuous moderate treatment is optimum, prolonged by heavy metal (C. C. G.)
12. **Seroresistance possibly represents** a biologic or metabolic state of the body (see Photinos on pluriglandular therapy, Bernard *et al.* on hypercholesterolemia, 1936) as well as an expression of persistence of the organism (Burke 1940, Kolmer 1936). Hence, in late latency after specific treatment has been carried out to the latency standard, nonspecific methods (ultraviolet light, autohemotherapy, milk injections, rest, iodides) may be considered, but fever is not advised (Stokes, Moore and Padget)
13. **Most observers,** especially European, largely disregard serologic fastness in clinically well persons after adequate treatment in whom examination and observation have failed to show active involvement. (Ravaut, Schulman and Levy, Jadassohn Handbuch, Wile, Scholtz, Spiethoff, Stumpke, Kerl.)
14. **Recall that ultimate reversal** of a seroresistant case to negative does not preclude progression, especially cardiovascular involvement under a cloak of seronegativity, or of progression or revival in nervous system or viscera (liver)
15. Conceding the nonconformity of the clinical material in the literature and the uncertainties introduced by multiple factors in treatment and infection, the seroresistant case may be estimated to have from 35 to 61 per cent prospect of reversal by an additional year of treatment with bismuth, or bismuth and an arsenical, or fever alone. The higher estimates suggest inadequate initial treatment rather than actual seroresistance.

The advances in our knowledge of seroresistance or reagin-fastness within the past decade are summarized in Fig. 210.

It would appear that as in latency in general, the more thoroughgoing the search of a supposed Wassermann fast case, the more likely is some grave

form of syphilis to be uncovered as a collateral or underlying manifestation Nothing therefore, could be more ill advised than casual assurance to Wassermann fast patients that their positive blood tests have no meaning Painstaking investigation suspended judgment, and observation over a long period are therefore indispensable to the interpretation of fixed positive serological tests.

On the other hand, it must be recalled that most material was gathered from sick rather than well population, so to speak, and that it would therefore tend to collect the graver aspects of serological resistance rather than the more benign forms. That this may be an important consideration is suggested by Ravaut comment on Schulmann and Levy discussion of the fixed-positive Wassermann. Waltz, inspired by his chief, Ravaut, made an extended survey of the serological status of elderly veterans at Ivry with respect to the existence of positive serological tests with no other manifestations of the disease. While the figures are apparently not yet published Ravaut believes that the positive Wassermann in old age and the positive Wassermann as such, as manifestation of syphilis in the established infection, should be minimized. He feels that many of these elderly persons could well congratulate themselves that they had not been subjected to treatment test of reversibility which might easily have injured their viscera and left them in worse state by far than that of possessors of mere positive serological tests.

Wassermann-fastness in Latency—The Cooperative Clinical Group with Moore as spokesman finds that once the patient achieves true latency the proportion of patients obtaining "satisfactory" results from treatment is approximately the same whether the patient remains Wassermann-fast or undergoes permanent serological reversal to negative

Reactivation after Treatment.—The paradoxical result of increasing the positiveness and resistance of a serological test by treatment which often clears up other symptoms when present, is not a rare experience. Especially since the inauguration of bismuth has it become not uncommon to see weak positives converted into strong positives which may ultimately subside after a delay of months or even years. In prenatal cases particularly one may observe this reactivation or provocation of a serological test which becomes irreversible. Without any exact figures to offer we have, nonetheless, observed such a reactivation to be the predecessor of interstitial keratitis and are inclined to regard it as a symptom of revival of the infection for which treatment should be thorough and persistent even if ultimate reversal to negative does not ensue. In this connection bismuth "lag" (Chapter VI) should be recalled

German opinion, as expressed in the Handbuch summary and subsequently (1934) as collected by the Dermatologische Wochenschrift, attaches relatively little clinical importance t this state maki g it entirely matter of individual judgment whether or not such patients shall be periodically treated, continuously treated, allowed to marry or t conduct their lives otherwise without reference to their serological status. French opinion, collected in the discussion of Schulmann and Levy paper disclosed majority opinion similar to the German view Schulmann and Levy themselves opposed extended treatment, preferring observation and serological tests at three months intervals with spinal fluid examination once year R vaut tended to minimize the monosymptomatic serological test and to believe that clinical considerations and good sense should settle treatment decisions in all such cases, rather than the outcome of laboratory procedure Pautrier supported the same view Galliot has pointed the question by an account of two treatment disasters which he believed had resulted from attempted yearly and persistent treatment of patient with monosymptomatic Wassermann-fast conditions. Tzanck and coworkers (1934) insist that regular and intensive treatment from the start does way with serologic fastness.

On the other hand, Sézary insisted that resistant serological tests mean visceral syphilis and emphasized the importance of thoroughgoing search. Gougerot distrusts fixed-positive cases and advises against their marriage Louste does not interdict marriage but considers it matter

for individual judgment whether t treat or not. Moutbur emphasized the necessity for great conservatism in permitting the marriage of women with monosymptomatic positive Wassermann reactions, saying that in series of such patients observed in his clinic, not one had been able to give birth t healthy child, in spite of treatment during pregnancy amounting in some cases t as high as 10 Gm. neoarsphenamine. In English-speaking countries, Burke has insisted that no such condition as Wassermann-fastness need exist in effectively treated early syphilis, managed by the alternating continuous scheme. Kolmer believes that fixed-positive serological tests mean active foci and indicate periodic treatment throughout the persistence of the condition, if not through life. Wile in an excellent expression of his views deplores the overtreatment of serological irreversibility believing that much damage is done thereby and that the panic which too often arises physician and patient under such conditions should be controlled by rational considerations. At the same time, progression, especially in the direction of cardiovascular syphilis, under the mask of monosymptomatic seropositive latency must be carefully watched. Seropositive latency in the man is to some extent different problem from that in the woman, for the birth of syphilitic child, even in seronegative latency is form of relapse whose frequency is as yet unknown. With Ravaut, we believe that the consideration of clinical indications and good sense will allow age and time factors to decide the issue of treatment rather than the serological test as such when latent syphilis is recognized in the later years of life.

Treatment *of* Serological (Reagin) Fastness.—Courses which should secure the maximum effectiveness in the prevention of serological fastness in early syphilis are outlined in Chapter XIV Serological fastness of the monosymptomatic type in latency should first be weighed by the criteria and methods applicable to latency in general (p 440) If after an application of these principles, it seems proper to treat or to prolong the treatment of the absolutely monosymptomatic latent case at all, we should say that a six months rest period—followed by not less than three courses of an appropriate bismuth salt and a year of iodide on a two months on two months off schedule—could be regarded as a therapeutic test of the reversibility of the serological reactions as such. This, too, would in a previously untreated monosymptomatic case constitute a treatment for life insurance which in all probability would disturb the immunity balance of the latent patient as little as possible. The use of the arsenicals for this purpose should be given second place and be contingent on very careful consideration of age and time factors and of the question of pregnancy as a possibility In young men and women within the marrying and childbearing age, asymptomatic seropositive latency should as has been said, be treated with something approaching the intensity of early syphilis in the effort to secure a reversal.

If these measures fail, and it is believed necessary to go farther with the matter especially in the younger and more robust patients, various methods in addition to the suggested use of bismuth, now finding current support in the literature and in practice will be found summarized in Fig. 211 Of all the steps mentioned, evaluation, rest period, and change of the mode of attack by changes of drug, either singly or in combination, are the basic essentials.

Bismuth is probably the most effective drug at present available, the results secured by various authors ranging from 34 to 75 per cent reversals with from one to four courses of the drug.

We have had several favorable experiences with boiled milk. It is, we believe a serious question whether fever therapy is justifiable in dealing with monosymptomatic cases except as a sequel of inappropriate or inadequate treatment in young adults. The experience of Kemp and Stokes was favorable (46 6 per cent reversals) so far as immediate results were concerned, using typhoid-paratyphoid vaccine but it should in all cases be followed up by bismuth for relapse is usually prompt

Vigorous repeated ultraviolet irradiation combined with injections of autogenous blood (autohemotherapy) has been successfully employed by Rajka and Radnai since 1929 for the treatment of resistant syphilis, including serologically fast patients and patients with cardiovascular and neurosyphilis. The blood injections were employed for their additional desensitizing effects, as suggested by the experimental work of Pörtök, Lehner and Rajka. On the other hand, Ambrosio found that ultraviolet, roentgen-rays, radium, cobalt, and nickel had influence on the results of the Wassermann test. The observations of Rajka and Radnai were, however in part confirmed by Gottron at the Copenhagen Congress in 1930. Rajka and Radnai emphasize that to be successful the treatment must be intermittent, not more than 30 irradiations in series, and the autogenous blood being drawn half an hour after the treatment and reinjected intragluteally or intracutaneously. The irradiations were given three times a week, and the amount of

Fig. 211

RECOGNIZED METHODS OF TREATING WASSERMANN FAST PATIENTS

1. Preventive
2. Evaluation (complete examination) and expectancy with periodic (usually annual) reexamination and quarterly tests.
3. A rest period. The test may become spontaneously negative in three to twelve months and remain so, especially after bismuth and fever
4. Change of drug. This is probably the most important element in the whole range of possibilities (Burke, Belding, Stokes *et al.*)
5. Rest followed by change of drug (Burke, Tobias)
6. Bismuth—regarded as specially effective by Grund, McCafferty and MacGregor, Belding, Sutton, Levin and Schwartz, Tobias *et al.*, probably an example of (4)
7. Bismuth arsphenamine sulphonate (Kolmer, Stokes, Miller and Beerman).
8. Sodium iodide intravenously (Burke, Vercellino, Beinhauer, Schwartz and Beerman) 1 to 10 Gm. daily 10 per cent solution (intravenously)
9. Sodium thiosulphate (hyposulphite) intravenously 10 to 20 cc. of 20 per cent solution for 12 to 15 injections (Ravaut, Flurin, Beinhauer and Jacob, Werlagick, see Tobias *et al.*) Also with addition of Lugol's solution.
10. Milk injections (5 to 10 cc. milk boiled five minutes) or Aolan once or twice weekly intramuscularly alone or with alternating injections of bismuth (Burke, Greenbaum and Wright, Stokes)
11. Autohemotherapy. Physiotherapy (ultraviolet light)
12. Balneotherapy—sulphur baths, Turkish bath (Burke, Prosser White, Cady and Everhardt)
13. Fever therapy—with sulphur in oil (Schroeder, Flurin), Ducrey vaccine (Gougerot, Sézary *et al.*, Burke), typhoid-paratyphoid vaccine (Kemp and Stokes), malarial therapy
14. Experimental and unevaluated method
    (a) Pluriglandular therapy. Total dosage of various mixtures ranging from 1.2 Gm. of the more active (thyroid) to 12 Gm. of the less active preparations (ovary) by mouth or injection (Michaelides and Kloukinis, Photinos)
    (b) Irradiation of the spleen (Gougerot)
    (c) Cerium compounds (Bertillon)

INDIVIDUALIZE EACH CASE OF WASSERMANN-FASTNESS. IF ENTIRELY ASYMPTOMATIC, OBSERVATION NOT TREATMENT MAY BE THE ONLY NEED

blood withdrawn ranged from 2 to 15 cc. and totalled 20 injections. The positive Wassermann reaction became negative in 50 per cent of cases of latent syphilis in which previous chemotherapy had failed to secure reversal, and in 28 per cent of patients with resistant Wassermann reactions in neurosyphilis. It remained negative for from two to thirty-six months. About 50 per cent of the cases ultimately became positive again. Gottron commended the method as one suitable for employment in patients rendered syphilophobic by their persistent positive serological tests. The constitutional and tonic effects are excellent.

Serological Fastness with Visceral and Other Lesions.—Wassermann-fastness as an expression of visceral, vascular and neurosyphilis becomes, relatively speaking, a secondary matter. The object in all such cases should

be to secure the best possible symptomatic results for the patient, and the type of treatment and drugs employed must be absolutely dependent upon the major symptomatic indications and the rules for treatment of the structures involved rather than on any considerations affecting the positive serological test. It may be expected that approximately 50 per cent of visceral and vascular syphilis will become serologically negative in the course of the appropriate treatment for the condition. The residuum of 25 to 50 per cent should be treated rather by the clinical indications in the case, under expert direction, than by the mere fact of a persistent positive serological test. It would, to our minds, for example, be quite inexcusable to subject cardiovascular syphilis to fever therapy in the effort to secure a negative blood regardless of the general status of the case.

Serologic Fastness Under Intensive (Five-Day to Ten Week) Therapy for Early Syphilis.—The conditions governing intensive therapy result in a gradual decline in seropositiveness after the administration of the indicated amount, as shown by quantitative serologic procedure. Most of the available data are thus far for the five-day to ten-day method. By the fourth month after the initiation of treatment, the patient should be lastingly seronegative and most patients with early syphilis become so by the eighth to twelfth week. Hyman and coworkers (1939) report one case (6 per cent) doubtfully positive after five years Leifer Chargin and Hyman (1941) reported 9 cases of seroresistance in 386 treated with five-day arsenotherapy eight of them in the small dose mapharsen series. According to Elliott, Baehr Shaffer Usher and Lough, the largest series of five-day cases thus far published showed 3 to 20 per cent seropositive after 6 to 12 months, depending on the stage at which treatment was begun. If the titer of reagin rises sharply after a period of decline, a relapse has occurred and the patient is retreated. Adequate information on latency and so forth is not yet available.

"Cure" and Arrest in Serological Fastness.—Serologically fixed positive cases are subject to the same rules with reference to the interpretation of cure and arrest as are all latent cases. They should not be dismissed from observation throughout life. Treatment, especially with the arsphenamines, once begun should be carried through a heavy-metal phase to avoid reactivation of the infection. The widest differences of opinion may justly exist on the advisability of maintaining a state of latency by periodic treatment, and the field of speculation is easily wide enough to embrace the almost diametrically opposite opinions already reviewed.

GENERAL HYGIENE OF SYPHILIS

The first step in a general hygiene of syphilis is the complete establishment, so far as possible of rapport between physician and patient and the adequate instruction of the latter at the very first interview in regard to the general nature of the disease, the problems which treatment will inevitably raise and the course which the patient should pursue to protect his lif and his associates to the greatest possible degree from unfavorable consequences of his infection. After the diagnosis is conclusively established, the necessary time should be taken to lay before the patient the points outlined in Fig 212. At no time in the life history of the disease or of the patient is he so open to impressions, to intelligent influence and to a frank, dispassionate statement of the facts. The term "first interview" must not be too literally interpreted

Vigorous repeated ultraviolet irradiation combined with injections of autogenous blood (autohemotherapy) has been successfully employed by Rajka and Radnai since 1928 for the treatment of resistant syphilis, including serologically fast patients and patients with cardiovascular and neurosyphilis. The blood injections were employed for their additional desensitizing effects, as suggested by the experimental work of Pertik, Lehner and Rajka. On the other hand, Ambrojio found that ultraviolet, roentgen-rays, radium, cobalt, and nickel had influence on the results of the Wassermann test. The observations of Rajka and Radnai were, however, in part confirmed by Gottron at the Copenhagen Congress in 1930. Rajka and Radnai emphasize that to be successful the treatment must be intermittent, not more than 30 irradiations in a series, and the autogenous blood being drawn half an hour after the treatment and reinjected intragluteally or intracutaneously. The irradiations were given three times a week, and the amount of

Fig. 211

RECOGNIZED METHODS OF TREATING WASSERMANN-FAST PATIENTS

1. **Preventive**
2. **Evaluation** (complete examination) and expectancy with periodic (usually annual) reexamination and quarterly tests.
3. **A rest period.** The test may become spontaneously negative in three to twelve months and remain so, especially after bismuth and fever
4. **Change of drug.** This is probably the most important element in the whole range of possibilities (Burke, Belding, Stokes *et al.*)
5. **Rest followed by change of drug** (Burke, Tobias)
6. **Bismuth**—regarded as specially effective by Grand, McCafferty and MacGregor, Belding, Sutton, Levin and Schwartz, Tobias *et al.*, probably as an example of (4)
7. **Bismuth arsphenamine sulphonate** (Kolmer; Stokes, Miller and Beerman).
8. **Sodium iodide intravenously** (Burke, Vercellino, Beinhauer, Schwartz and Bussman) 1 to 10 Gm. daily 10 per cent solution (intravenously)
9. **Sodium thiosulphate** (hyposulphite) intravenously, 10 to 20 cc. of a 20 per cent solution for 12 to 13 injections (Ravaut, Flurin, Beinhauer and Jacob, Werlinich, see Tobias *et al.*) Also with addition of Lugol's solution.
10. **Milk injections** (5 to 10 cc. milk boiled five minutes) or Aolan once or twice weekly intramuscularly alone or with alternating injections of bismuth (Burke, Greenbaum and Wright, Stokes)
11. **Autohemotherapy**, Physiotherapy (ultraviolet light)
12. **Balneotherapy**—sulphur baths, Turkish baths (Burke, Prosser White, Cole and Everhardt)
13. **Fever therapy**—with sulphur in oil (Schroeder, Flurin), Ducrey vaccine (Gougerot, Sicard *et al.*, Burke), typhoid-paratyphoid vaccine (Kemp and Stokes), malarial therapy
14. **Experimental and unevaluated methods**
    (a) Pluriglandular therapy. Total dosage of various mixtures ranging from 1.2 Gm. of the more active (thyroid) to 12 Gm. of the less active preparations (ovary) by mouth or injection (Michaelides and Kleanthis, Photinos)
    (b) Irradiation of the spleen (Gougerot)
    (c) Cerium compounds (Bertillon)

INDIVIDUALIZE EACH CASE OF WASSERMANN FASTNESS. IF ENTIRELY ASYMPTOMATIC, OBSERVATION NOT TREATMENT MAY BE THE ONLY NEED

blood withdrawn ranged from 2 to 15 cc. and totalled 20 injections. The positive Wassermann reaction became negative in 80 per cent of cases of latent syphilis in which previous chemotherapy had failed to secure reversal, and in 28 per cent of patients with resistant Wassermann reactions in neurosyphilis. It remained negative for from two to thirty-six months. About 30 per cent of the cases ultimately became positive again. Gottron commended the method as one suitable for employment in patients rendered syphilophobic by their persistent positive serological tests. The constitutional and tonic effects are excellent.

Serological Fastness with Visceral and Other Lesions.—Wassermann fastness as an expression of visceral, vascular and neurosyphilis becomes, relatively speaking, a secondary matter. The object in all such cases should

nation by the physician himself. Such leaflets are best used to supplement viva voce instruction, and for this purpose we have often had intelligent patients read the sections on the control of infectiousness and personal hygiene in our own text. A lay substitute for the physician, as for example, social worker may give the instruction, but this method think is inferior both in its influence on the patient and on the rapport between physician and patient which proper technic of presentation usually establishes. The method, none the less, can be made effective in clinics by competent social service chief and organization.

Diet, T bacco Alcohol.—Diet, being regulated to no small degree by the prevention of reaction, is discussed on page 869 The use of tobacco, formerly interdicted for many years, has lost much of its significance for relapse and recurrence with the institution of modern treatment. Like advice on sex matters, honoring in the breach rather than the observance is to be expected today and if the patient pursues treatment consistently little attention need be paid t the matter The chewing of tobacco is more deleterious than the smoking from the standpoint of exciting local lesions, and positive danger in the later years of the disease lies in the development of leukoplakia.

While the occasional case may require touch of horrific management, patients with late syphilis of nondefections type should not be made the victims of needlessly ascetic régime. Alcohol has been discussed as provoker of complications, but there are many other reasons which we believe more or less inevitably make the syphilologist, who views his problem broadly an antagonist of the liquor traffic (*pace facta*, regardless of his reaction toward Constitutional prohibition as such. The general effect of the use of alcohol varies through the widest possible range in different individuals, so far as their syphilitic infection is concerned. One sees on the one hand persons of the most exemplary even abstemious make-up, carried away by the worst complications *of the disease, and on the other born convivialists and gone-the-ropes sots, escaping with* comparatively benign syphilitic infections. The weight of tradition is against permitting patients with syphilis t use alcoholics, and with this tradition our experience is, in the main, in accord.

Sex Hygiene of the Syphilitic Patient.—In matters of sex hygiene the physician may advise—in his professional capacity he too often proposes but the patient disposes—the exercise of continence throughout the infectious years of the disease. The bearings of this problem on marriage in particular are more fully discussed under syphilis and marriage, page 1069 Where it is expected and in fact, where it is not expected that the patient will be amenable, it is the duty of the physician to warn specifically against all forms of intimate contact to instruct the patient, if the sumptuary laws too generally on the statute books permit, with regard to the mechanical protection of himself and *his partner in sexual intercourse. The most shocking and disastrous* denouements have followed a mistaken adherence to serological criteria of infectiousness, the seronegative patient either taking the law into his own hands or being permitted by his physician to have unprotected intercourse once his Wassermann became negative. The principles on this matter should be carefully reviewed (p 166)

The effect of irritation from excessive sexual intercourse in women in promoting the development of infectious genital lesions is well known. Cleanliness, surface disinfection, and reduced activity are therefore proper management. There is, however no other evidence that the living of the ordinary normal sexual lif materially affects the course of syphilis in one way or another. The excessive sexual activities of the paretic patient may underlie family crises and contribute somewhat by exhaustion, perhaps, to the deteriorative process. Similarly the impotence of late neurosyphilis may give rise to troublesome situations and may often be quite as much psychological as organic. Certain forms of treatment, such as tryparsamide, *are reported by patients to have* directly stimulative effect on sexual activity and priapism and jaculatory disturbances may accompany lower-cord irritation or follow intraspinal therapy Patients who are undergoing sexual revivals under the tonic effect of treatment should be warned to stay within bounds. The fear factors, particularly in the case of an uninfected partner may be seriously disturbing to normal sexual function.

The Importance of Rest.—Rest is one of the potent and often life-saving factors in the general management of the syphilitic patient.

In a disease such as syphilis, involving wide ramifications throughout the patient's physical and mental life rest must include more than mere sleep important though this is. Reduction of irritation and overstrain contributes greatly at times to the favorable progress of a syphilitic infection, especially if there is an involvement of the nervous system. Eight hours sleep a night, two of them before midnight temporary relief from business pressure by an out-of town trip the breaking of a prolonged treatment siege by judicious rest periods and lazy vacations à la Izaak Walton, have marked therapeutic worth. The practice of breaking the day in the middle by half an hour of complete relaxation lying down with a short nap is life-saving in many patients in the middle and late forties or fifties even if there be no active disease of the cardiovascular system to compel it. Rest in bed is of value in patients with greatly reduced physical reserve or local lesions, if they are kept irritated by movement or hypostatic congestion. The occasional undoubted value of a "milk cure with its weeks of rest in bed and forced feeding with gain in weight is by no means to be despised. Routine sedation, especially with barbiturates and bromides is to be discouraged psychotherapy encouraged.

Locus Minoris Resistentiae.—The patient should be instructed and managed with respect to the weakest part of his organization, always the favorite site of attack by a syphilitic infection. The liver and nervous system of the alcoholic, the cardiovascular and particularly the coronary mechanism of the hard-pressed business man and physician, the brain of the intellectual worker the ankles and knees of the tabetic, the bones and skeletal tissues of the laborer and the person subject to physical accident must all be borne in mind for protection against injury and overload, lest their weakest spots become the sites of syphilitic lesions.

The Mental State of the Syphilitic Patient.—Regimen undoubtedly has its good effects, and the emphasis thus far given to a disciplined management of the disease may perhaps have overstated them. The physician should however avoid the tendency to surround his patient with petty restrictive prohibitions or to create an atmosphere of therapeutic asceticism On the other hand, some patients, in their eagerness to cooperate, demand precise and multiplied instructions, and these should be gently persuaded away from their penchant for regulation.

Syphilophobia.—The phobic mentality finds one of its most distressing fields of activity among syphilitic patients. Syphilophobia is less a product of syphilis than an evidence of a constitutional trend of mind which leans toward hypochondriasis in one direction or another Most of these patients are markedly vagotonic, subject to vasomotor crises, and sometimes literally psychotic though not necessarily as a result of their syphilitic infection A careful appraisal of the situation will sometimes show the syphilophobia to be merely a fixation expressive of some deeper-lying complex situation in the patient's mental life When this is the case, no amount of argument or persuasion seems capable of correcting the situation without, perhaps, neuropsychiatric intervention. On the other hand, the average syphilophobe terrorized by hearsay or unfortunate contacts with the literature of the subject, can be not infrequently completely disabused of his notions by thoroughgoing authoritative consultation. In dealing with such patients the consultant must not for a moment allow his presuppositions and instinctive diagnosis to dominate his approach to the case He must conduct the most thoroughgoing examination and, in fact insist on the carrying through of every procedure which will resolve a doubt to say nothing of creating a conviction in the patient that no

stone has been left unturned. Thus managed, with the full armament of syphilological investigation discharged against the patient's fears, the most remarkable and satisfying restoration to confidence and activity takes place both in patients who have and who do not have the disease.

Apart, however from the distinctly phobic group of mental and nervous disturbances, the successful management of the day-to-day mental problems of the "normal" syphilitic patient calls for both a deep and a broad humanity In no disease does the ministry of the physician perform a more needed service, or achieve more gratifying responses. It is precisely in the patients whom one most desires to help that the opportunity for human as distinguished from purely professional service comes. The mental state of the finer types of patients with this disease still reflects the stigmatization which has so long marked the superficial and unthinking world attitude toward sexual problems. Some of them are, of course, painfully almost repellently persistent in their reiteration of the disgracefulness of their situation and their surroundings. For such patients, immutable in their sackcloth and ashes, little can be done. On the other hand, a large proportion of patients are readily responsive and deeply appreciative of the help of the physician in reorienting themselves toward their situation and recovering their self-respect. They make not only mental but surprising physical responses, which are entirely unattainable until the root of the situation has been touched

The idea that he is lost, that foul and gross decay waits him, that he can never marry that insanity is certain, that his wife, if he has one, will disown him, is tragically real to many patient. The time and patience spent in explaining way and correcting these mistaken notions are part of the actual treatment of the disease. In dealing with such patients, we quot them figures as exactly as we can and illustrate with parallel cases outside the range of the patient acquaintance. W invite the patient on the service to look about him and note the wrecks who come in and restored men and women who go out. Nearly always, in his search, the hope that is instinctive, leads the patient to find someone worse situated than himself who has recovered, and his own return to confidence ensues. This is one of the great advantages of managing syphilis in the aggregate—"there none so worse but there worser.

Anxiety Neuroses.—True anxiety complexes are not uncommon in syphilis and must be painstakingly unraveled and set right with psychiatric assistance if necessary The patient who shows a persistent depression or failure to respond is not always suffering from a syphilitic cerebral process, although cortical vascular degenerations do produce deceptive imitations of anxiety neuroses. When the trouble is finally unearthed we find it wise to be systematically encouraging to anxious patients, although without sacrifice of the ultimate truth if in the end it must be told. It is not, of course wise or necessary to throw all prognostic caution to the winds, and he who does so has only to travel a short distance before the facts overtake him and end his prestige. But the value of an honestly hopeful but clear and conservative statement to the patient cannot be overestimated.

Family Problems—the Tradition of Secrecy—The question as to whether or not the patient—often the innocently infected member of the family—shall be informed as to the diagnosis has many aspects. Undoubtedly occasions arise in which damage may be done by informing an introspective and phobic individual or one deeply imbued with the moralistic conceptions of syphilis as a punishment for vice, of the fact that he or she has the disease. On the other hand it is extremely difficult to secure cooperation from a patient not informed as to the situation and particularly is this so when an intensive form

In a disease such as syphilis, involving wide ramifications throughout the patient's physical and mental life rest must include more than mere sleep important though this is. Reduction of irritation and overstrain contributes greatly at times to the favorable progress of a syphilitic infection, especially if there is an involvement of the nervous system. Eight hours sleep a night, two of them before midnight temporary relief from business pressure by an out-of town trip the breaking of a prolonged treatment siege by judicious rest periods and lazy vacations à la Izaak Walton have marked therapeutic worth. The practice of breaking the day in the middle by half an hour of complete relaxation lying down, with a short nap is life-saving in many patients in the middle and late forties or fifties even if there be no active disease of the cardiovascular system to compel it. Rest in bed is of value in patients with greatly reduced physical reserve or local lesions if they are kept irritated by movement or hypostatic congestion. The occasional undoubted value of a "milk cure with its weeks of rest in bed and forced feeding with gain in weight is by no means to be despised. Routine sedation, especially with barbiturates and bromides is to be discouraged psychotherapy encouraged

Locus Minoris Resistentiae.—The patient should be instructed and managed with respect to the weakest part of his organization, always the f vorite site of attack by syphilitic infection. The liver and nervous system of the alcoholic, the cardiovascular and particularly the coronary mechanism of the hard-pressed business man and physician, the brain of the intellectual worker the ankles and knees of the tabetic, the bones and skeletal tissues of the laborer and the person subject to physical ccident must all be borne in mind for protection against injury and overload, lest their weakest spots become the sites of syphilitic lesions.

The Mental State of the Syphilitic Patient.—Regimen undoubtedly has its good effects, and the emphasis thus far given to a disciplined management of the disease may perhaps have overstated them The physician should however avoid the tendency to surround his patient with petty restrictive prohibitions or to create an atmosphere of therapeutic asceticism. On the other hand, some patients, in their eagerness to cooperate, demand precise and multiplied instructions and these should be gently persuaded away from their penchant for regulation.

Syphilophobia.—The phobic mentality finds one of its most distressing fields of activity among syphilitic patients. Syphilophobia is less a product of syphilis than an evidence of a constitutional trend of mind which leans toward hypochondriasis in one direction or another Most of these patients are markedly vagotonic subject to vasomotor crises, and sometimes literally psychotic though not necessarily as a result of their syphilitic infection. A careful appraisal of the situation will sometimes show the syphilophobia to be merely a fixation expressive of some deeper-lying complex situation in the patient's mental life When this is the case, no amount of argument or persuasion seems capable of correcting the situation without, perhaps, neuropsychiatric intervention. On the other hand the average syphilophobe, terrorized by hearsay or unfortunate contacts with the literature of the subject, can be not infrequently completely disabused of his notions by thoroughgoing authoritative consultation. In dealing with such patients the consultant must not for a moment allow his presuppositions and instinctive diagnosis to dominate his approach to the case. He must conduct the most thoroughgoing examination and in fact, insist on the carrying through of every procedure which will resolve a doubt, to say nothing of creating a conviction in the patient that no

gation, may have a catastrophe of the first magnitude on his hands. It was the occurrence of situations such as this which led the Mayo Clinic to adopt a standing rule that none should communicate the diagnosis of syphilis to the patient except the Syphilologic Section, which could do so after a full investigation of its authenticity

SYPHILIS AND INTERCURRENT DISEASE

Syphilis is so often detected in the course of examination for other ailments and without any special or apparent relation to the patient's chief complaint, that special consideration should be given to certain interrelations and to the treatment appropriate to the circumstances.

Syphilis and Diabetes.—Unquestionably from the literature, the published experience of experts in diabetes, the examination of diabetics with concomitant syphilis, and the experience of syphilologists, diabetes due to syphilis, if it exists at all, is a rarity Diabetes in persons with syphilis which responds curatively to treatment for syphilis is likewise a rarity· so great a rarity in fact, that the huge experience of Joslin and his coworkers cannot record a convincing case. Diabetes is clearly therefore not a parasyphilitic disease as some overenthusiastic proponents in the first several decades of the eighty-year-old discussion were inclined to suggest. It is possible that a syphilitic who becomes diabetic has become so because of his syphilis, though far more probably independently of it. The broadening conception of the causal glycometabolic mechanisms involved permits the belief substantiated by occasional cases, that syphilis of the nervous system may have a diabetic accompaniment or consequence as well as syphilis of the pancreas. The incidence of syphilis in diabetics is, by the criteria used approximately that in the population at large the relations of the disease to the known causes of diabetes mellitus probably minimal and insignificant. In general, the diabetic with syphilis, laboring as he does under a double disadvantage, should, first of all, be proved a diabetic by rigid test criteria, and then should have his diabetes dealt with independently of the fact that he has syphilis. To what extent coexistent syphilis aggravates diabetes is not clearly known though there are speculations relative to the roles of arterial injury and the general effects of infection on diabetics which lead to the belief that syphilis aggravates diabetes. In therapeutic tests to determine the importance of the syphilitic factor if such exists, in a given diabetic case, occasional striking improvements in glycosuria, and even its occasional complete disappearance under antisyphilitic treatment, have been observed. This, it must be admitted, does not establish beyond question, the syphilitic origin of the diabetes. Elmer and Kedzierski, and most recently Joslin, McDaniel and Marks, have emphasized that the mere disappearance of glycosuria does not establish the cure of diabetes but that restoration of blood sugar and carbohydrate tolerance to normal and a raising of the renal threshold of sugar elimination are all necessary parts of the demonstration of a causal relationship when an apparent diabetic recovers under treatment for syphilis. In only six of 258 cases studied by the last mentioned authors could an even plausible case for the true syphilitic origin of the diabetes be made out, when such criteria were applied, and they and Williams and Kitchell likewise have emphasized the conclusion that prolonged observation after the improvement of the glycosuria does not tend to indicate that the "cure" of the diabetes is actually established. Generally

speaking then, a syphilitic with diabetes should be treated for his diabetes by the most modern criteria and methods. His tolerance of antisyphilitic treatment under these conditions is, according both to our experience and that of Moore satisfactory Therapeutic test results cannot be accepted on their immediate face, but must be evaluated after prolonged observation by those competent to study the diabetes as such

The literature of the syphilis-diabetes question is bumpy with controversy and occasional polemicism. Probably the ablest summary completely covering the early literature was that of Lemann in 1929 Warthin and Wilson precipitated an angry reaction against their often misquoted and over-emphasized statement that changes produced by syphilis in the pancreas might make it an important factor in pancreatic diabetes. It is only fair to say that uncritical examination of the diabetic side of the question has been matched by equally uncritical examination of the syphilitic side on the part of students of diabetes. The revolution now occurring in serologic diagnosis of syphilis will probably considerably modify our conceptions of syphilis as an intercurrent disease but certainly something more than a single and not infrequently hypersensitive serologic test on the blood or "history of infection must be offered as an adequate evaluation of the syphilis recognized in diabetic individuals. Until such evaluation is complete with large autopsy material t back it, syphilis-diabetes relationship will remain a field for opinion rather than for proved fact, and one can base his opinion on choice of views gained from yet incompletely evaluated material. The trend of opinion is as above described.

Some hesitation in the use of bismuth in the treatment of syphilitics with diabetes is developing from the observations of Epstein; Corson, Decker and Williams (1940) and Peters (1942) of the Johns Hopkins Clinic that bismuth, like lead, may be mobilized in the circulation with increased risk of toxic effects under conditions of acidosis. Such an observation would seem only to point t the necessity for placing the diabetic with actual or threatened acidosis under a properly regulated diet and insulin therapy before beginning intensive administration of heavy metal

Syphilis and Tuberculosis.—The interrelations of syphilis and tuberculosis present a picture of confusion and opinionation slowly resolving itself into definitive and valid principles in much the same fashion as is taking place in the diabetic field. Much the same criticisms of the available material in the literature apply to both problems. Tuberculosis is evaluated and treated by experts in tuberculosis, while syphilologists have a relatively small hand either in the diagnosis or in the selection of therapy on syphilologic principles. The coincidence of syphilis and tuberculosis offers many opportunities for diagnostic confusion, as pointed out by Padget and Moore (1936) There are striking diagnostic resemblances in the histopathology of the two diseases autopsy evaluation leads more easily to a recognition of tuberculosis than of syphilis up to and including late latency and late syphilis itself In the field of pulmonary tuberculosis versus pulmonary syphilis, the majority of observers are agreed that differentiation is impossible except in congenital syphilis, other than by exclusion. Syphilis is known to exert accelerating or unfavorable effects on the outcome of other forms of pulmonary disease as for example in delayed resolution of pneumonias. Relatively seldom is an adequate search for both diseases conducted at the same time in the same person. According to Goldblatt (1939) this may result in the overlooking of one-half of the tuberculosis in the tuberculous individuals, and one-seventh of the syphilis in the syphilitic individuals. Serologic tests for syphilis, almost the sole criterion of diagnosis of the disease in many of the older series, have a definite margin of nonspecificity (about 8 per cent, Parran and Emerson, 1939) with the increasing knowledge of the incertitudes of the positive serologic reaction, it is possible that the margin of error in the diagnosis of syphilis in tuberculous individuals by serology alone will become larger rather than smaller thus diminishing still further the conclusiveness of the old literature on both diagnosis

and treatment. The nonspecific effects of treatment for syphilis, particularly with the arsphenamines, on tuberculous processes (Chapter V) interfere materially with therapeutic test interpretation. While this type of interpretation has not as yet proved to be of importance in pulmonary tuberculosis, its actual significance is unknown. It would appear therefore that the foundation for exact evaluation of the influence of syphilis on tuberculosis and of treatment for syphilis on both diseases, when simultaneously or successively present, does not as yet exist.

The more recent literature, despite evidently increased attention to these considerations, still contains flat contradictions difficult to explain. Padget and Moore (1930) utilizing their own and Turner's experience with Johns Hopkins material, conclude that the coincidence of tuberculosis and syphilis seems less frequent than expectancy under the laws of chance whereas Goldblatt (1939) in an even larger material, concluded that syphilis appeared to have a predisposing influence on tuberculosis which became particularly manifest in the older age groups. Their material indicated that there was more tuberculosis per thousand patients with prior syphilis than per thousand without prior syphilis. Rather tending to support the belief that tuberculosis is either more prevalent or more serious or both in individuals who have had syphilis, are Hall's actuarial figures frequently cited in which the mortality of a group of persons thoroughly treated for syphilis was notably higher (147 per cent) than in nonsyphilitic individuals pulmonary tuberculosis, pneumonia and cancer being the outstanding causes of the higher mortality

Current figures for the coincidence of the two diseases range from Turner (1930) (Johns Hopkins syphilitic out-patients) 1 0 per cent and Trail (1939) (British experience) 1 42 per cent, to 3 6 per cent Goldblatt (1939) (Shoemaker Clinic, Cincinnati) 4 per cent Warring (1939) (Laurel Heights Sanitarium Connecticut) and 3.5 per cent, Berg (1937–39) (Seaview Sanitarium Staten Island) Berg, separating Negroes and whites, found 4.5 per cent for the former 2.5 per cent for the latter The Negro figure is notably higher in other estimates including the National Tuberculosis Association survey of 4 1 per cent white and 21 per cent Negroes. Murphy and Bromberg (1941) obtained closely comparable figures of 5 4 per cent white and 17 4 per cent Negroes.

The combination of syphilis and tuberculosis requires more thorough going analysis on the basis of the age and type of both infections. Most of the large-scale statistical material deals with pulmonary tuberculosis, in which classification is on the basis of the NTA formula of far advanced moderately advanced minimal and extrapulmonary while the classification of the syphilis, when not serologic and over-burdened with doubtful reactions, is largely that of late syphilitic manifestations (Warring for example) ranging from late congenital to neurosyphilis, with an enormous preponderance of late latency It would seem therefore that most of the material to date, while it may have high individual significance, has thrown relatively little light on the serious public health problem of the person with active tuberculosis who simultaneously presents active and infectious syphilis. Padget and Moore's (1936) criticism of the tendency to consider tuberculosis the more important of the patient's ailments, is well taken, and justifies their insistence that both diagnosis and treatment should be individualized, supervised and conducted by experts as Joslin and his coworkers have pointed out for diabetes. The problem of how to manage early syphilis in the presence of early pulmonary tuberculosis assumes increasing importance because of the current use of

collapse therapy which maintains an infective or potentially infective syphilis in active circulation, so to speak. There is therefore particular need to study the influence of early syphilis upon tuberculosis acquired simultaneously or immediately subsequent to the syphilitic infection, and vice versa, and the influence of intensive treatment for syphilis upon the progress of tuberculosis especially in its earlier and more active, as distinguished from its fibroid, status.

On this question, the invocation of animal experimental technics has been emphasized by Padget and Moore with concessions as to the unsatisfactory state of the evidence thus far. Ohsawa (1922) whose conclusions have been mentioned previously has observed that rabbits previously infected with tuberculosis have a general increase in resistance to syphilis, and that testicular tuberculosis in syphilitic rabbits progresses more rapidly than in controls. A much more penetrating study of the question by Aronson and Menasse (1938, 1940) based upon the pathologic histology in the experimentally inoculated rabbit, indicates that in the syphilitic rabbit the local inflammatory reaction following the injection of tubercle bacilli into the skin is more intense in character, has more distinctly vascular and hence more extensive distribution, and the tuberculous lesions resemble in their histologic characteristics the primary and secondary lesions of syphilis rather than the characteristic lesions of tuberculosis, even though *Treponema pallidum* cannot be identified by darkfield. Their observations suggest that the subsequently induced (by inoculation) tuberculosis excites the so-called anamnestic reaction in which the second infection, in addition to provoking an antibody reaction against tuberculosis, also provokes antibodies (or reaction mechanism) against the initial infection (syphilis). It would thus seem that under certain circumstances both provocation of the infection and an actual contribution to its conquest by the body can be made by the second or subsequent infection, at least when that second infection is tuberculosis. Much more extensive work, however is still required for the substantiating of such conclusions and all such studies must be subject to the notable differences between syphilis and tuberculosis both in the rabbit and in man.

The general conclusion supported by the observations of Norris and Landis (1933) Gallant (1929) and others, that syphilis unfavorably affects the course of tuberculosis can be set over against the views of Schlesinger (1926, 1932) which have markedly influenced the technic of treatment, to the effect that active tuberculosis seems to modify in a favorable direction the course of the syphilitic infection. Some of the irreconcilabilities will probably be resolved by the point of view emphasized by Padget and Moore (1936) that mass statements on these matters are untrustworthy and that the status of infection in the individual, and the individual's type or degree of reaction to it, as evaluated by experts, would probably furnish the only safe basis for a rational therapy. This has been in the main our own view of the problem. Nicolas and his coworkers, as previously cited pointed out very clearly as regards the nonspecific effect of the arsphenamines on tuberculous processes, that their influence is dependent upon the individual's reaction to the tuberculous infection at the time treatment was instituted. If resistance to the tuberculous process was good or on the increase, treatment effect from the arsphenamines was satisfactory whereas if the tuberculosis was progressing unfavorably the same arsphenamine therapy hastened the decline.

The Treatment of Syphilis Complicating Tuberculosis.—Schlesinger's rules, which seem quite largely to have dominated American practice, adopt four classifications as follows

1. Late syphilis, nonprogressive clinically complicated by recent pulmonary tuberculosis, in which the tuberculous process takes precedence and antisyphilitic treatment is delayed until the tuberculosis lesion has been stationary for several months. Arsphenamines and iodides are avoided.
2. Untreated late syphilis with old fibroid pulmonary tuberculosis in which

arsphenamine may be used in small doses but the risks of fever therapy are unjustifiable, unless paresis is imminent or the tuberculous lesions wholly insignificant.

3. Old stationary pulmonary tuberculosis with early syphilis, in which, if fibroid, the arsphenamines may be used, but cautiously if cavitation is present, watching for signs of progression of the lung lesions. Here Schlesinger lays down the principle, still a matter of controversy though supported by numerous case observations including especially those of Padget and Moore, that the arsphenamines (and particularly 606) can produce grave reactivation with hemoptysis and dissemination of pulmonary tuberculosis.

4. Early syphilis with recent tuberculosis, the most unfavorable combination of all, in which, if the syphilis is not overwhelmingly endangering the patient, antisyphilitic treatment should be limited to the heavy metals, until the tuberculosis is completely controlled.

These basic rules, while in the main supported by current experience, are subject to some important modifications. First, from the experimental side Aronson and Meranze concluded that local experimental tuberculosis pursues an identical course in untreated syphilitic rabbits and in syphilitic rabbits treated with treponemicidal doses of arsphenamine. McDermott, Webster and McCrae (1941) in treating two control series of tuberculous rabbits, one syphilitic and one nonsyphilitic, found that arsphenamine failed to produce demonstrable ill effects on the tuberculosis and that roentgen-ray shadows present in the majority of tuberculous animals almost totally disappeared during the course of treatment in both treated animals and controls.

To the clinical evidence favoring more thorough-going treatment for syphilis than the disease is usually accorded in tuberculous patients, Berg's large series (1927–1939) appears illuminating. In 372 patients, active treatment of syphilis by arsenical injection exerted little or no influence in activating a latent or quiescent tuberculous lesion. Antisyphilitic treatment with arsenicals in submaximal doses did not affect adversely the course of active pulmonary tuberculosis except in terminal cases. The coexistence of syphilis, whether treated or untreated, with pulmonary tuberculosis, did not conduce to a more rapidly fatal course. Exudative lesions in the lungs apparently resolve more frequently in patients treated with arsenicals for coexisting syphilis than in patients not treated. The sputum of patients who were treated with pneumothorax became negative more often when arsenicals were administered for coexisting syphilis than when not so treated. Neither syphilis nor arsenical injections affected adversely the progress of therapeutic collapse therapy. Syphilis, treated or untreated, did not interfere with the healing of thoracoplastic wounds. Hydrothorax, following pneumothorax, occurred slightly more often in patients receiving arsenical injections for syphilis than in those not receiving arsenicals. There was no evidence that chronic or latent syphilis favored fibrotic changes or that the administration of arsenicals or heavy metals interfered with fibrosis. The bacillary content of the sputum impressed Berg as being as good a criterion in judging the status of pulmonary lesions in syphilitic patients as in nonsyphilitic individuals.

Even on the disputed question of the effect of iodide traditionally withheld in tuberculosis because of the widely accepted though incompletely supported view that it promotes the softening and resolution of fibrous tissue and hence interferes with the encapsulation of tuberculous foci, Berg's experience was radical. The administration of large doses of potassium iodide (in one case)

did not inhibit the favorable progress of tuberculous exudative lung lesions and calcified nodules in the bronchial nodes and lung parenchyma.

Warring, with a series of 106 patients (1939) found that the course of syphilis in patients with tuberculosis did not differ materially from the course of the disease in the nontuberculous He adopted four rules, taking account of various factors in both diseases, which may be quoted as follows

1 If the syphilitic disease is in an infectious stage treat it to the point of noninfectivity no matter what the extent or type of the tuberculosis.

2 Should the syphilis be in the latent stage, attention should be paid first to the age of the patient. Patients over sixty can usually be safely allowed to forego antisyphilitic treatment. If the patient is younger evaluate the pulmonary disease. Do not treat patients with far-advanced progressing tuberculosis who appear to have a hopeless prognosis If the far-advanced disease later shows definite evidence of improvement, antisyphilitic treatment can be started cautiously Delay treatment in patients with acute active or exudative types of tuberculosis no matter how small the extent of the tuberculosis. Treat patients with previously active pulmonary disease as soon as it becomes quiescent.

3 In patients with certain early manifestations of active late syphilis (aortitis aneurysm central nervous system syphilis) treat the syphilis if it is felt the patient s life may sooner be endangered by syphilitic infection than by his chronic pulmonary tuberculosis Whereas treatment of syphilis can be delayed in the latent syphilitics while the progress of the tuberculosis is observed it should be begun at the earliest possible moment in patients with active late syphilis

4 Suspend treatment of syphilis if the patient has febrile reactions, hemoptyses develops wet pleurisy or shows, by x rays spread of tuberculosis.

These two groups of observations with the rules deducible from them express in the main the most recent opinions as to the treatment of conjoint syphilis and tuberculosis As reviewers of the problem we would tend to emphasize first the importance of considering the public health aspects of the patient combining active infectious syphilis with any stage of tuberculosis equally with any patient presenting active tuberculosis coincidently with syphilis. The current use of ambulatory methods greatly increases the danger of the distribution of both infections through the community if adequate case-finding and case-holding procedure (follow up) is not employed and early control of infectiousness in syphilis practiced. It would seem therefore that early infectious syphilis, if it is judged unwise to treat it with the arsenicals, should be controlled by sanitarium care.

The improvement in arsenotherapy of syphilis introduced by mapharsen and the arsenoxides makes it safer to use them than was previously the case with the arsphenamines Padget and Moore s (1936) group of unfavorable cases for example may be in part attributable (aside from their conceded influence of coincidence) by their use of 606 the most "pneumotropic" of all the arsenicals (see Chapter VII) The experience of Astrachan and Wise (1938) Warring (1939) and Murphy and Bromberg (1941) with mapharsen has confirmed the reasonable expectation that it would be a materially less reaction-producing and safer drug in the treatment of syphilis in combination with tuberculosis than the arsphenamines. The remaining rules above cited are part of the general principles of syphilotherapy—to treat the more threatening ailment first, and with the greater emphasis to employ caution in preventing therapeutic

shock and paradox where the syphilis is active or of a late focal type in important structures and to employ bismuth which appears thus far to be devoid of unfavorable effect, where there is reason to fear the more rapid action of an arsenical. Our own experience tends to indicate that one of the safest guides to caution in therapy is fever and that the febrile tuberculous patient who is progressing unfavorably will probably respond unfavorably if not disastrously to vigorous treatment for his syphilis particularly with an arsphenamine. With respect to fever therapy there is agreement (Schlesinger Padget and Moore ourselves) that it is dangerous and may reactivate any type of tuberculous lesion, no matter how completely quiescent it may appear to be on clinical examination.

The foreshortened intensive (five-day to twelve-week) systems for the treatment of early syphilis (see Chapter XIV) should not, with our present knowledge, be employed in the treatment of clinically tuberculous individuals

The use of iodide in tuberculous subjects is a controversial topic in which their avoidance is the more conservative course In therapeutic tests, the nonspecific effects of the arsphenamines on tuberculous processes must constantly be borne in mind, and heavy-metal therapy if necessary with mercury (soluble salt intramuscularly) may need at times to be invoked for a decision Even under these circumstances the effect is not absolutely specific (see Fig 499)

Syphilis and Malaria.—The coexistence of these two diseases and the use of malaria in treatment create an important problem All of the heavy metals with the addition of antimony and gold had, according to Cole and coworkers (1940) been shown to influence the behavior of malaria induced or otherwise. Goldman (1938) Cleveland and Turvey (1939) Young and McLendon (1939) Solomon Epstein and Berk (1033) Whitehead and Dorey (1941) and many other observers have testified to the effects of the arsenicals on malaria. Whitehead and Dorey and Goldman specifically even rated mapharsen as far more effective than quinine in quartan infections, and notably more effective than arsphenamine and neoarsphenamine. He employed mapharsen for the termination of tertian malaria in place of quinine. Young and McLendon in examining these statements, took pains to control their use of arsenoxide and tryparsamide for the termination of quartan malaria by reexamination of blood smears as long as twenty-two weeks after the completion of the mapharsen course and found all their patients had become asymptomatic malarial carriers Three of their quartan malaria patients who received tryparsamide, examined one year after the completion of tryparsamide treatment still showed *P malariae* in the bloodstream It is apparent therefore that where syphilis and malaria coexist, the arsenicals cannot be relied on to terminate the malaria. The action of bismuth in the control of malaria coincident with syphilis has been discussed in Chapter VIII and in connection with malarial therapy The effects of the thio-glycolate suggested by Schwartz (1939) on the malaria, seems to be the most pronounced. Winckel (1941) from a large experience emphasizes that neoarsphenamine may modify the behavior of a malaria and render it asymptomatic without ridding the blood of plasmodia. It cannot be used to replace quinine for therapeutic effect. It would appear therefore that where the coexistence of the two infections is demonstrated or suspected quinine must be employed to evaluate and eliminate the malarial factor

Syphilis and Febrile Disease.—Fever is a not uncommon symptom of syphilis in all stages and the disease unquestionably acts to prolong the febrile

phase of acute and chronic infections though it does not necessarily contribute to the elevation of the temperature. McLester has noted this in typhoid fever it is a well-known occurrence in the postcritical persistence of fever after pulmonary infections occasionally modifies the temperature curve of malaria and may influence the behavior of chronic sinus infection. Intercurrent syphilis in malignancy especially of the liver may be obscured in diagnosis by a low persistent fever which responds to treatment for syphilis giving the impression of a false therapeutic test.

Syphilis and Septic (Streptococcal) Infection.—Since the occurrence of apparently false positive serologic reactions in subacute bacterial endocarditis is now reasonably established, therapeutic confusion may arise from the influence of treatment for syphilis in the presence of this and other forms of septic infection Le Cocq (1936) reported on the usefulness of neoarsphenamine in serious staphylococcic infections.

Experimental studies by Osgood, Brownlee and Joald (1940) (*cf* Osgood, 1942) using the marrow culture method, have indicated that the effects of the sulfonamides and arsenicals are dependent to some extent on the strain of the organism, and that in some types neoarsphenamine and mapharsen are markedly more effective than the sulfonamides, especially against *Strep. viridans* A blood concentration of six parts per million of the drug must, however be maintained constantly over period of twenty-four to seventy-two hours or longer This requires at body weight of 60 kg total of 0 4 Gm. in divided doses of 0 1 Gm. each at 8 a.m., 11 a.m 2 p m. and 6 p.m. Every subsequent day 1.0 Gm. is given at 8 a.m 3 p m., and 10 p.m., and on the third day and subsequently the blood arsenic levels will indicate the necessary continued dosage. The blood arsenic determinations followed the Rankston, Magnuson and Chaney technic (1940) Mapharsen is less uniformly effective than neoarsphenamine. Regard must be had for the higher mortality of this intensive type of arsenical administration but the risks are regarded as justified.

Nongummatous septic foci should be treated surgically though if the condition of the patient is good, one or two preliminary doses of neoarsphenamine may facilitate the surgical management of the case and protect the staff in the case of an active recent syphilitic infection. In symptoms associated with gummata and with gummatous visceral processes simulating septic infection, especially in the liver treatment for syphilis produces prompt relief of symptoms while surgery may cause exacerbation (see Fig 665) Neoarsphenamine, recommended by Casuto Reucker and Chetwood in pyelitis was found by Buchtel and Cook from the Mayo Clinic, to be particularly helpful in infections of the urinary tract of coccal origin but not in bacillary pyelonephritis.

This should be of some importance in the treatment of tabetics who have complicating pyelonephritis, but for number of undetermined reasons, actual experience with the pyelonephritic tabetic is less encouraging than with other types. The drug fails in the presence of stones, marked obstruction, severe focal infection infection referable t Strep. fecalis, nonspecific prostatitis and chronic cicatricial pyelonephritis. Acidification of the urine improves the result. Small doses, interestingly enough, are as efficacious as the larger ones, and improvement will occur after the first or second injection if it occurs t all.

Syphilis and Other Spirochetoses.—Syphilis complicated by other spirochetoses, including Vincent spirillosis and pulmonary spirochetosis and pulmonary gangrene, may yield confusing therapeutic results. In Vincent infections in the mouth and throat with fever and destructive lesions suggesting rapidly progressive late syphilid, mapharsen and neoarsphenamine must be locally applied for best results. Ducbz, Weismuller, MacIntosh, Cooper and Tatum (1936) rate mapharsen as at least as effective as neoarsphenamine when used locally employing swab of 1 per cent solution of the drug with gargle of 0.4 per cent of the drug an intravenous injection of 30 mg. of mapharsen for the initial dose, and three successive intravenous injections of 60 mg. each at four-day intervals. An alkaline gargle is recommended to clear the mucosa of secretions before the mapharsen mouth-wash is employed. Rosebury Foley and Rights (1939) had discouraging results with neoarsphenamine in experimental pulmonary infections of guinea pigs, but

in man we have observed occasional clinical responses so striking as to suggest diagnosis of pulmonary syphilis. Landau, Pego and others found that clinical nonspecific improvement would take place even though the flora of the sputum presented no organisms of the fusospirillary type. The recognition of the virus pneumonias is too recent for the evaluation of the effect of antisyphilitic treatment upon them, but the unfavorable effect particularly of 606 on nasorespiratory infections with pulmonary complications (precipitation of pneumonia) should be kept in mind.

Syphilis and Arthritis.—Patients who have syphilis complicated by arthritis usually tolerate the arsphenamines well and, in fact, may derive both nonspecific and specific improvement from them. In the nonsyphilitic arthritides, however, the improvement is limited and seldom lasting, so that we have given up the effort to treat these patients nonspecifically by arsenicals in the absence of syphilis. Several reports such as that of New and Brittingham (1938) emphasize the frequency of syphilis as factor in polyarthritis, especially among Negroes in the South, in opposition to Turner's estimate of its relative infrequency in this race. Patients with arthritis tolerat mercury poorly and particularly mercury by inunction. The effect of bismuth in arthritic conditions is not yet evaluated.

Syphilis and Hypertension.—The patient with essential hypertension, in our experience, tolerates moderate treatment for syphilis well, especially if he can be kept at rest in bed which, of course, temporarily reduces his tension. Permanent ffect in the form of reduction of blood pressure sometimes results. Iodide intravenously does not seem to accomplish anything unusual for these patients. Mercury especially in the form of the insoluble salts, seems less well borne than normally It is very important that patients with rising (especially diastolic) blood pressure and coincident syphilis should be early advised and treated in preventive way for the vascular condition, fact which is apt to be overlooked by enthusiastic syphilotherapists. Reductions in weight, lowered protein and salt intake, calcium, and suitable rest and exercise should be prescribed in detail.

Syphilis, Nephrosis, and Nephritis.—The arsenicals are so well tolerated by the kidney that there need be no reasonable hesitation in using them for therapeutic tests to determine the syphilitic character of nephritis, or in the tonic treatment of concomitant syphilis. Mercury if carefully used by inunction, will not induce more than transient irritation. Under no circumstances should it be given in the form of an insoluble salt intramuscularly Bismuth, because of its much less irritative effect on the kidney is now accepted as preferable to mercury in practically all cases, except possibly those complicated by syphilitic heart lesion (see p. 209). In early syphilis complicating severe nephritis the low nephrotoxicity of the arsenicals dictates their choice. Neoarsphenamine is more nephrotoxic than 606 and there have been two reports of death from nephritis complicating mapharsen therapy rated, however, by Levin and Keddie (1944) as of small significance. A close watch must be kept of the spinal fluid for signs of neurorecurrence. Patients with a late syphilis and chronic nephritis should be treated or not in accordance with the individual indications, and with regard for life expectancy and infectiousness rather than the abstract desire to treat syphilis.

Syphilis and Pernicious Anemia.—This is dealt with in the suggestions and recommendations made on page 415.

Syphilis and Goiter.—Goiter patients with syphilis sometimes constitute serious problem. Where the basal metabolic rate is found to be definitely above normal (plus 20 or over) and the syphilis is not acute or infectious, operation is advised before treatment for syphilis is begun. The hyperthyroid patient is, in our experience, definitely and often explosively reactive to the arsphenamines, and it is much better to get him int condition to receive adequate treatment for his syphilis than to treat him without attention to the complications. On the other hand, it is worth remembering that the nervous and mental symptoms of the hyperthyroid patient may be closely simulated by those of patient with neurosyphilis and coincident goiter with slightly elevated basal metabolic rate. In such patients, in whom the full appraisal of their syphilis was not made before operation, the most violent reactions may occur pseudohyperthyroid delirium with delusions and mania, often bearing the distinctive paretic stamp. When the basal metabolic rate was not high, treatment for syphilis in such patients before operation has produced marked improvement in mental symptoms. It has, in fact, sometimes entirely dispelled the mental picture of hyperthyroidism. In all goiter patients with coincident syphilis as detected by the blood Wassermann test, and slight or moderate increase in basal metabolism, spinal fluid examination is desirable before operation. This does not, of course, apply to cases of obvious and marked hyperthyroidism as indicated by their basal metabolism, for whom operation as soon as possible is clearly essential. Netherton (1934) from the experience of the Cleveland Clinic, believes that syphilis alone can produce symptomatic pictures simulating hyperthyroidism. His review of the literature is the most complete to date. He concludes that antisyphilitic treatment should not replace surgical intervention in cases of active hyperthyroidism in syphilitic individuals, as opera-

tion followed by antisyphilitic therapy will prevent the cardiac damage which may result from unnecessary delay. Syphilis does not interfere with convalescence in these cases. Where preoperative treatment is advisable, as it often is, it should not be too intensive. Patients having neurosyphilis associated with hyperthyroidism are poor surgical risks, especially if there is mental deterioration. Preoperative antisyphilitic treatment in these cases is indicated, and is of default value especially in cases of tabes dorsalis. Gummatous thyroiditis, which we have seen operated upon before the Wassermann test was taken, must, of course, not be overlooked, although it is comparatively rare. It responds well to treatment and operation is thereby rendered unnecessary. The caution against iodide in patients with adenomas of the thyroid should be repeated. We have seen several patients with syphilis develop hyperthyroidism under treatment for syphilis, though the responsibility of the treatment was not apparent.

Syphilis and Hypothyroidism.—J. H. S. has seen one example in which the raising of the basal metabolic rate to normal in a hypothyroid patient resulted in a temporary but remarkable gain in mental acuity without treatment for syphilis. The mental picture was that of the depressed, degenerative phase of general paresis, and the spinal fluid was typically paretic. It is fair to infer that a low basal metabolic rate in syphilitic patients requires the same attention as in others. We have no records of patients with syphilis who have had low basal metabolic rates, to show the effect on hypothyroidism of treatment for syphilis.

Syphilis and Nonspecific Mental Disease.—Wezberg (1940) review of the problem of syphilitic psychoses, by demonstrating the complexity of the problem and especially of the diagnosis of general paresis on clinical grounds emphasizes by implication the unreliability of symptomatic therapeutic test results in the treatment of syphilitics with psychoses which may or may not be syphilitic. (See Chapter XX.) The treating of syphilitic patients with nonsyphilitic mental disease depends upon the general outlook of the case from the standpoint of life expectancy, infectious contacts, and the assumption of family or sexual responsibility. We have seen no evidence of any distinctive contraindications in limited experience. If the patient is likely to be returned to society, neglect of his syphilis while in the psychopathic hospital may make him a later source of danger to the public or to his immediate contacts.

The Value of Routine Serological Tests and Preoperative Arsphenamine.—It is impossible to overemphasize the worth of routine serological tests in placing the physician and surgeon on guard against risks which they may be obliged to assume but which they need not assume unawares. If it were more generally realized that operative procedures of other than an emergency character can be fully protected even in syphilitic patients by the preliminary administration to the patient of 1 or 2 small doses of an arsphenamine within forty-eight to seventy-two hours, the very serious existing risks for certain types of surgical work might be materially reduced. While certain clinics, such as that of Rochester, Minnesota, have only a relatively small amount of syphilis in their clientele and an exceedingly small proportion of it in the infectious stage of the disease, other operative clinics, especially in the field of gynecology and otolaryngology and obstetrics present a varying proportion of extremely serious risks. Student services in large cities in which women are delivered with relatively little warning and under unfavorable conditions should especially be controlled by the routine predelivery blood test for syphilis. Needle-prick infections have the reputation, largely due to Almkvist's study of "syphilis d'emblée" of being direct blood-stream infections without the warning of a chancre.

Postoperative Antisyphilitic Treatment.—While recommending the protection of the surgical staff by the preliminary administration to the patient with syphilis of two or three arsphenamine injections, it is essential to point out that as soon as convalescence is established, treatment should be pressed with the skill and determination that will bring about an ultimate cure or arrest, if possible. Too often the recognition of an intercurrent syphilis leads to the mere perfunctory giving of two or three "shots" after operation by a surgeon to satisfy a vague sense that a little something ought to be done

Fig. 213.

TO AVOID PROFESSIONAL INFECTION WITH SYPHILIS

Suggestions for the Physician

1. Demand routine preoperative and predelivery serological tests. An emergency Kline (elimination test) can be done in thirty minutes.
2. No barehand work about mouth, throat, or genitalia.
3. Nursing personnel trained to responsibility about pricked gloves.
4. Wear glasses.
5. Break finger-to-face or -nose habits.
6. Keep the mouth shut.
7. Look before entering.
8. Suspect *on your own person, the "won't-heal" lesion, the solitary lymph node* (*satellite* bubo), the indolent "infection"—especially fingers.
9. Do your thinking before, not after, a needle prick (see Fig. 214)

ABOUT NO ASPECT OF SYPHILIS IS THE PHYSICIAN OR SURGEON AS CRASSLY IGNORANT AND NEGLIGENT AS ABOUT HIS OWN INFECTION

Fig. 214.

IN CASE OF SUSPECTED ACCIDENTAL INFECTION WITH SYPHILIS IN MEDICAL PRACTICE

1. **You should know beforehand, not after,** if possible, the risks you are assuming. Routine serological tests in medical preoperative and obstetrical examinations, thorough inspection of mucosae, anus and genitalia, palms and soles, and a carefully taken history will largely protect you from unforeseen risks.
2. **Interpret the risk assumed,** before or after the accident, as follows:
   (*a*) The older the infection in the patient, the less the risk to you—after five years it is practically nil, even though his serological tests be positive. Old latent, gummatous, cardiovascular and neurosyphilis is harmless.
   (*b*) Nose, throat, and genital work is the most dangerous. Direct inoculation of blood is very dangerous only in the patient with early syphilis (first two years)
   (*c*) Recent arsphenamine treatment (up to within one to three months) usually renders the patient harmless. The earlier the case the more treatment is desirable.
   (*d*) Within forty-eight hours after an adult dose of an effective arsphenamine, a patient is temporarily harmless ("preoperative sterilization")
   (*e*) A lapse of hours greatly reduces the worth of any prophylaxis after injury; a lapse of more than a day or two renders it worthless and even dangerous ("asymptomatic carrier").
3. **If in the light of these considerations,** quickly reviewed, you believe yourself to have run significant risk of infection, proceed as follows:
   (*a*) Lay the site of the injury wide open immediately and rub in calomel ointment, 33 per cent in equal parts of lanolin and lard, for five minutes by the clock.
   (*b*) Take a "base line" *serological test on your* blood.
   (*c*) Repeat the serological test weekly for one month, biweekly for two months and then monthly for six months.
   (*d*) Some experts advise a spinal fluid examination at the end of the year, even if seronegative.
   (*e*) If the delay was too great or the risk so great as to amount almost to certainty of infection, consider outright treatment for syphilis, *versus* observation as in serological follow-up.
   (*f*) Remember that needle pricks may give rise to direct blood stream infections, and do not depend merely on watching for a local lesion.

about the syphilis. Such a course is too obviously criticizable to require comment. It frequently leaves the patient in a worse state than he was at the

outset with respect to the disease The following case is an example of this situation

Mr F H aged thirty-four years, complained chiefly of vomiting spells. He gave a history of early syphilis. Physical examination was negative. A test meal showed hyperacidity: roentgenograms of the stomach were negative. Pupils were sluggish to light, but not fixed. Serum Wassermann reaction was negative A preoperative diagnosis of chronic cholecystitis and chronic appendicitis was made and verified at operation. Relief of symptoms did not follow the operation, however and the patient was then given 2 injections of arsphenamine on suspicion, but without appreciable result. Seven years after operation he returned, stating that he had had no relief from his symptoms. The blood Wassermann reaction at this time was again negative, but spinal fluid examination showed positive evidence of syphilis of the nervous system. A diagnosis of tabetic neurosyphilis with gastric crises was made and systematic intensive treatment with arsphenamine and mercury resulted in striking improvement.

If, in view of the history of infection and sluggish pupils, a spinal fluid examination had been resorted to in the face of a negative Wassermann reaction at the time of operation, this patient's tabes could probably have been completely arrested. The two arsphenamine injections given to satisfy a feeling that something ought to be done for the suspected syphilis accomplished nothing for the patient, although the fact that his crises were amenable to treatment was subsequently demonstrated.

SYPHILIS AND TRANSFUSION

The enormous increase in the use of blood transfusion as a method of medical and surgical treatment increases while the use of stored blood (blood banks) plasma, and frozen and desiccated serum tends to diminish the risk of the transmission of syphilis The reported incidence of transfusion syphilis is in ludicrous contrast to a reasonable estimate of its frequency Rein, Wise and Cukerbaum (1938) estimated sixty-eight cases in the literature, while a fair syphilologic estimate of at least four cases known to each of 550 syphilologists in the United States would make the frequency pyramid upwards from a minimum of 2000 cases *The reluctance to report an ignominious flop* which is having increasingly serious medicolegal consequences, will probably obscure indefinitely the actual incidence of this type of medical catastrophe

The fundamental principles involved are relatively simple, and have applicability in simple clinical rules. The biologic aspects of the syphilitic spirochetemia have been considered in Chapter I. The organisms may be present in the blood within a few hours after inoculation throughout the period of active early manifestations, including chancre and secondaries and on into the period of latency Serologic tests for syphilis are known to be negative during at least the earliest part of this spirochetemic phase and this fact alone limits their value as protection against the transmission of the disease by transfusion. Physical examination of the seronegative subject may disclose the presence of a primary lesion in the seronegative phase, but on the other hand, such a lesion may be inconspicuous or even nonexistent. Since syphilis may be acquired at any time during the life of a professional donor periodic serologic testing as well as periodic physical examination is useless as a preventive The only resort is blood test and examination immediately before the drawing of blood. Rein Wise and Cukerbaum (1938) have shown both the necessity for and the simplicity of a unit procedure covering simultaneously blood typing and the detection of syphilis, utilizing the ultrasensitive Kline exclusion technic whose simplicity and rapidity is such that the entire work-up of the transfusion donor including his immediate physical examination need not occupy more than thirty minutes No laboratory which examines the blood of donors can be considered completely equipped which

cannot carry out this procedure on every single donor and which does not provide a twenty four hour service for the purpose. The Kline finger puncture blood test procedure avoids the objection of donors to a double venipuncture

The advent of the blood bank and refrigeration and desiccation methods of handling pooled transfusion material tends toward relaxation of ideal precaution for the prevention of transfusion syphilis. Such relaxation is justifiably and vigorously opposed—first, because citrated blood when fresh is as effective in transmitting syphilis as whole blood. A storage of not less than forty eight hours (Turner and Diseker 1941) is necessary for the disintegration of the organism, and storage of four days or longer is the more desirable. It is apparent therefore that transfusion from blood bank unit, made up within the four-day period, which contains an increment of blood from syphilitic donor may transmit the disease. Refrigeration is a much less efficient protection than is generally supposed (Bloch, 1941) but survival of the organism after ninety-six hours at 4 Centigrade has been demonstrated. Even after ninety-six hours heavily infected blood like that of early syphilis may still be dangerous. Turner Bauer and Kluth (1941) found that *Treponema pallidum* and probably *Treponema pertenuis* are probably killed by the process of freezing and desiccation, even though by this method the viability of many bacteria and viruses is retained. Transfusions prepared from desiccated blood serum or plasma are probably without risk with regard to transmission of syphilis or yaws, even though the material is obtained from an infected donor

It must be clear therefore that the safe period for an infected blood or blood plasma cannot be less than four days after storage begins, and may well under some circumstances, especially refrigeration be longer

Emphasis on the occasional emergency situation in blood transfusion, less important since the use of banks, has led to number of suggestions for the destruction of *Spirochaeta pallida* possibly present, through chemical means. Kast, Peterson and Kolmer (1939) working with neoarsphenamine, demonstrated the safety of blood to which 10 mg of the drug per 100 cc. of citrated blood had been added. *Eichenlaub, Stolar and Wode (1941) suggested 10 mg.* mapharsen for each 500 cc. of sodium citrate, used in preparing transfusion blood. Quinine di-hydrochloride (Salkine, 1931) in 1 1000 concentration, has been suggested, but the storage time after the quinine was three days which may have resulted in self-sterilization of the blood

The use of cadaver blood has been advocated by Yudin (1936) where it can be available, t large centers, where the bodies of persons killed in traffic accidents and dying of thrombosis and angina pectoris especially can be available. Such blood can be stored for three weeks, but it would seem that the principles and objections pplicable to blood of living subjects are applicable to individuals recently dead.

As a statement of general principle, then, blood banks should contain only the blood of normal persons regardless of experimental work and protective bacteriostatic and spirocheticidal agents, the primary responsibility of those in charge of a blood bank is to see that the blood of syphilitic persons is excluded by every known test-precaution. The qualifying considerations above described, relative to period of storage and addition of spirocheticidal substances can have application only to emergency situations. There are unquestionably risks involved in attempting to protect any form of blood bank against contamination by *Spirochaeta pallida* by the addition of arsenoxide or an arsphenamine. There is therefore, no substitute to offer for the requirement of adequate blood serologic tests for syphilis for all donors on each and every donation of blood. Periodic taking of blood tests at *stated intervals* is not sufficient because it is clearly recognized that serologic tests may be negative even in the presence of spirochetemia in the incubation stage and early course of syphilis Every donor of blood for transfusion whether by bank or otherwise should, furthermore, be subjected to close physical inspection of the oral mucosa, trunk, anus and genitalia for the presence of suspicious lesions The only type of accumulation procedure for storage of

blood which can be regarded as literally free of risk of transmitting syphilis regardless of time factors is that of complete desiccation. Refrigeration alone cannot protect against every contamination possibility

It will be clear therefore that the gain in diminished risks of syphilis transmission by the newer developments in blood storage is relative and not absolute and that the precautions appropriate to direct transfusion and citrated whole blood are still in order

Medicolegally according t an opinion of the Burea of Legal Medicine and Legislation of the American Medical Association (1945), the liability of a physician who gives a transfusion with blood of a syphilitic donor the patient contracting syphilis, has not been fully explored by any court of ppellat jurisdiction. In the bsence of acut emergency the physician who uses untested blood of donor for a transfusion and thereby transmits syphilis t the recipient should be prepared in case of suit, t justify his actions by convincing evidence that in pursuing the course he did be xercised that reasonable degree of skill, knowledge and diligence ordinarily pos-

Fig. 215

DON'TS FOR BLOOD TRANSFUSION

1 Don't be panicked int calling a transfusion an emergency justifying slipshod consideration of syphilis, if thirty minutes for typing, physically examining, Kline finger-blood exclusion testing of donor is available.
2. Don't rely on a blood test alone t clude syphilis.
3 Don't cept member of th family as *pro facto* free of syphilis—even t mother and child. Check everyone even yourself The family member delusion is the worst pitfall of ll.
4 Don't trust any form of periodic test or examination of donors. Examination must be immediate, complete, before each donation.
5. Don't use banked blood stored less than four days.
6 Don t even in extreme emergency give an unchecked donor blood or seropositive latent blood (M Namara) without adding neoarsphenamine 10 mg. per 100 cc or mapharsen 0 01 mg. per 500 cc. Have it in your field kit.
7 Don t use kno n or suspected syphilitic or syphili seropositive blood for banks or plasma (unless desiccated)
8. Don't use th blood or body fluids of syphilitics, known or suspected, for any biologic treatment purpose (convalescent serum, et) unless effectively sterilized, or over five day old.
9 Don t fail t carry insistence on vigilance and detail in this matter out t the extreme periphery of our personnel, round the lock. Syphilis rides in on Default in the small hours.

sessed and exercised l *physicians under the same circumst nces, that is burden of proof* that physicians had better void rather than ttempt t meet. In the case of an acut emergency physician may be faced with the choice of using the blood of an untested donor thereby running the risk of transmitting syphilis t the recipient, or refusing t use the untested blood and thereby assuming the risk that his patient ill die because of that refusal When faced with such choice the alternative should be fully explained t the patient or t someone authorized t ct for him, leaving the decision t the patient or other responsible person to exercise his or her ow judgment n accepting or rejecting the blood of the untested donor The consent or rejection should if t all possible be reduced to writing. Where the patient cannot make a rational decision and where no other uthorized person is vailable to act in his stead the emergency being acut it is difficult t conceive of a court condemning physician for adopting necessary procedures t save a patient lif After all, syphilis curable lif extinct, is extinct. A California court has held that the paramount duty of physician is t save his patient lif even if some injury may result to the patient in the process.

As knowledge and facilities for the pplication of reasonable precaution to the protection of the patient receiving blood transfusion become more idely disseminated, standards more familiar nd the blunderingly inexcusable character of most of the mistakes made more apparent

the position of the physician who is responsible for the transmission of syphilis by transfusion will become increasingly and justifiably more precarious.

SYPHILIS AS A COMPLICATION OF SURGERY

This topic is of course repeatedly discussed from the diagnostic standpoint in subsequent chapters and is illustrated by numerous case examples. Patients with syphilis who have been effectively treated can be operated on with impunity. Untreated patients develop postoperative difficulties apparently attributable to their syphilis in from 7 to 10 per cent of cases exclusive of those in which the surgeon incised a gumma. Following operative trauma to an active gummatous lesion, which is tantamount to a diagnostic error on the part of the physician or surgeon, unfavorable results and an extension of the process may be expected.

Philip (1940) found that syphilitic patients, even though they had been treated with six arsphenamine injections, still showed nearly 10 per cent more wound infection than a control group of nonsyphilitics. Falk and Kempner (1941) confirmed this in a large series of laparotomies among Negroes, but believed the differences to be of small significance. Eviscerations and fecal fistulas in their experience had no apparent relation to the presence of syphilis, but they conceded that the latent form of the disease provides a slight additional risk as far as both wound healing and morbidity are concerned.

On the other hand, the behavior of the operative wound made in healthy skin even of undoubtedly syphilitic patients has been investigated by Goeckermann from Mayo Clinic experience and more recently by Scheffey. Both observers agreed that in the overwhelming majority of cases the surgical wound heals kindly and without complication attributable to the syphilitic infection.

Longstanding syphilis makes the patient a poor surgical risk in proportion as it affects his tissues and structures in general. He is no worse risk on this score than another patient with an equal amount of damage from some other cause. From the standpoint of the patient, an injection or two of arsphenamine before operation may or may not have an unfavorable effect upon his postoperative course. The case must be considered individually and the danger of setting up a therapeutic shock (Herxheimer) reaction, or doing damage to the cardiovascular or nervous system which will compromise the postoperative course must be considered. This, however, is not to be taken as minimizing the value of carefully considered adequate treatment for syphilis before operation in patients who do not present a surgical emergency. There can be no doubt that the large majority of patients with late syphilis can sustain operation for nonsyphilitic conditions without complications attributable to any effect of their syphilis. Goeckermann found that the chief difficulty in the relation of surgery to the untreated syphilitic patient was one of overlooking or not considering the syphilis in connection with the case as a whole and particularly with reference to diagnosis as illustrated by exploratory procedures. In 5000 surgical cases even a blood Wassermann test was taken in only 1600. The incidence of syphilis thus discovered was 0.46 per cent of the 5000 cases as against an expectancy for all the patients of the Mayo Clinic of more than 3 per cent. On the presentation of these facts to the Clinic it was made a rule that blood Wassermann tests were to be taken routinely on all patients before operation to assist in the recognition of gummatous

lesions and to make it possible to consider their syphilitic infection as part of their medical and surgical problem.

Wile (1938) has emphasized the importance of simultaneous antisyphilitic treatment in the surgical management of syphilitic osteomyelitis. He points out that gumma of the testis and gumma of the spinal cord are two notable exceptions to the rule that it is unwise to operate on purely syphilitic conditions. Both processes develop so rapidly that to anticipate their worst effects, operation should proceed, but be immediately followed by adequate treatment for syphilis. This is also true of gumma of the eyeball and osteomyelitis of the small bones of the head. Wile emphasizes cicatricial contraction as legitimate field for surgery in the presence of syphilis, and points out little recognized occurrence of plastic peritonitis, when abdominal operations are performed on latent syphilitics who have not been previously treated. Wiltrakis, Partipilo and Olsman (1941) found that surgical results in patients preponderantly with neurosyphilis presented somewhat higher mortality rate which on analysis, however did not seem to indicate that the risk in the neurosyphilitic is notably greater than in nonsyphilitics. Local surgical complications of the nature of wound infection, were more common in neurosyphilitics, but sloughing, evisceration and gumma formation did not occur If syphilitic patients had had adequate antisyphilitic treatment in the past, it provided the necessary insurance against bad effects without the necessity for further immediate treatment.

LOCAL TREATMENT OF SYPHILITIC LESIONS

The Chancre—The first principle of all local treatment of the chancre is a negative one. Do not make any applications other than physiologic salt solution or institute any systemic treatment for a suspected genital lesion, or in fact any genital lesion until a systematic and repeated search for *Spirochaeta pallida* has been made preferably by darkfield Excision of the chancre is neither necessary nor advisable, inasmuch as the removal of a merely incidental focus among the thousands of others already existent seems useless It is pointed out that the chancre is a site of recurrence at times, but we have not been able to convince ourselves that its recurrence is a solitary affair It is usually simply a part of a general recrudescence of the disease (For local treatment of other or complicating genital lesions see p 508 *et seq*)

Mouth and Throat Lesions.—Local treatment of mouth and throat lesions and the silver nitrate stick, against which Fournier spoke so frequently as a source of mediate transmission, have become unnecessary with the advent of the arsphenamines Ordinary cleansing measures are all that is called for between the time arsphenamine treatment is begun and the time the lesion heals. The disappearance of pain and secondary infection from a crateriform pharyngeal ulcer following arsphenamine treatment in a patient made cachectic by inability to swallow ranks with the astonishing transformations seen in the treatment of gastric syphilis.

Cutaneous Lesions.—Cutaneous syphilids rarely require more than a few days of wet dressings with potassium permanganate solution (1 4000) or boric acid solution, before healing takes place under arsphenamine In occasional extensive cases small clipped grafts may hasten the covering of denuded surfaces after the granulations have become clean. The noncontractile character of the syphilitic scar makes the deformity usually less than is expected. Thiocresol (Sulphen) may conceivably be employed to hasten granulation in large destructive or excavating syphilitic lesions but such steps are rarely necessary In fact, failure of a syphilitic lesion of the skin or subcutaneous tissue to heal with rapidity at once raises the question of malignancy rather than syphilis

Gummatous Lesions.—Osseous syphilids occasionally require the removal of sequestra for complete healing and special operative measures may be

needed in gummatous osteitis of the skull This should not be done until after treatment control is fully established, but, on the other hand should not be too long delayed The incision of gummas and their surgical removal is usually undertaken either on an error of diagnosis or under the mistaken conception that such lesions are the better for removal. Fibrous gummas of the meninges or brain may require removal as tumors With modern methods of treatment, operation on gummas in soft tissue except possibly the broken-down and septic gumma of the liver is usually needless and in fact, sometimes inexcusable

CHAPTER XI

THE DIAGNOSIS OF EARLY SYPHILIS—THE CHANCRE

The Diagnosis of the Chancre No Longer a Clinical but a Laboratory Problem.—The progress of venereology since 1904 has relegated farther and farther to the background the distinguished but one-sided French tradition of the morphologic diagnosis of the chancre. The clinical appearance of the primary lesion to which Fournier devoted so much descriptive eloquence remains a useful drill and a critical or collaborative instrument in what is no longer a clinical but a laboratory problem. Over-emphasis on the physical characteristics of the chancre has led in the past to innumerable errors of diagnosis. Leading all other determinants in the diagnosis of primary syphilis is the darkfield identification of *Spirochaeta pallida*. As an adjunct subject to critical interpretation, the positive blood serologic test for syphilis stands next. Bringing up the rear is the ancient fellowship of half-truths about induration, erosion, multiplicity, painlessness and so forth, which constitutes a clinical dialectic and occasionally assumes importance where no other help can be had but as a basis for diagnosis clinical criteria as such have gone to pot.

Today modern intensive therapy and the outlook for radical cure condemns unhesitatingly a system of diagnosis which, by increasing the value of the later instead of the earlier lesion, "loses the patient any part of his chance.

The art of morphological diagnosis in primary syphilis survives in those cases in which a concomitant syphilis is accompanied by nonsyphilitic lesions suggesting chancres. The diagnosis of chancroid, let it be emphasized, is no longer positive but negative despite the newer methods of diagnosis. It consists in eliminating syphilis.

Is the Chancre Becoming Rarer?—This question, inseparably linked with the epidemiology of syphilis, cannot be categorically answered. That there has been a decline of infectious syphilis of the primary and secondary types has been attested by the experience of the University of Pennsylvania Clinic, the Cleveland City Hospital Clinic and numerous observers speaking informally. Reiter (1934) found that in the German Navy there had been a 45 per cent decrease in primary and secondary syphilis since 1927. Lomholt records that in Denmark fresh infections fell from 4500 in 1919 to 700 in 1933 (1935). Blakley and Levin (Cleveland 1938) found that from a peak of 419 new infectious cases in 1926, there was a steady drop to a low of 92 in 1937. Chancroid on the other hand, wavered up and down between limits of 190 and 11 over the same period. Lymphogranuloma venereum, coming to recognition as a disease in 1931 by Frei test, ran a steady 80 to 90 cases per year to 1937. The experience of the University of Pennsylvania clinic shows a drop in the percentage of infections to all other types of syphilis seen between 1931 and 1941 inclusive from 24.4 to 8.9 per cent. In 1942 an unexplained 4 per cent rise occurred. The experience of individual clinics is so obviously conditioned by special circumstances affecting their clientele that almost any figures can be matched against their opposites in various parts of the country and various countries of the world.

The question of what has become of early infectious syphilis is too complex to be answered by any one set of figures. The partition of the case material between private practice and clinics varies with economic conditions and with the interest in and ability of the private practitioner to hold and treat, if only for a short period, the primary syphilis brought to his attention. There is some reason to suspect that primary syphilis is at intervals replaced by infectious relapse in the infectious syphilis category as the result of the inadequate treatment of early syphilis which presents itself to the practitioner and which he cannot hold to adequate treatment. The incidence of symptomless infection is a riddle as yet answered only by individual speculation. The question

is being raised as to whether the initial lesion of syphilis and the secondary eruption are really disappearing from the field of medical practice or whether some change is taking place in the disease itself, or some result being secured by dissemination of knowledge regarding treatment, which is gradually causing these outspoken manifestations to become increasingly rare. In comparing notes with other clinicians there is a general agreement, which our own experience confirms, that the early manifestations are being seen in clinics less frequently than they were ten years ago. Part of this may be attributed to the actual decline in the incidence of syphilis as a disease which is indicated by such statistical estimates as are appearing in the English and German literature. Part of it, no doubt, comes from the readier use of the arsphenamines by the practitioner whose patient no longer reaches the clinic until he has had at least 1 or 2 injections. Part of it may conceivably be due to a change in the disease itself, which may be productive, on the one hand, of less conspicuous early manifestations, and, on the other of more frequent involvement of the nervous system. The recognition of extragenital lesions, so far as we have observed, seems not to have kept pace with the identification and consequent disappearance of the genital chancre, a point also noted by Morton Smith. The inconspicuous genital chancre, the syphilis without chancre, the "bubon d'emblée," and the extragenital undiagnosed chancre seem distinctly more numerous than in the past by contrast with the apparent decline of the genital lesion.

Fig. 210.

THE PHYSICAL CHARACTERISTICS OF THE PRIMARY LESION OF SYPHILIS

1. The chancre tends to be single rather than multiple
2. It has a relatively long incubation period (twelve to forty days)
3. The lesion if uncomplicated tends to be relatively painless (chancre of the finger may be an important exception)
4. There is induration of the base of the lesion.
5. Erosion of the surface is the rule rather than ulceration.
6. The border tends to be sharply defined, shows a fine hemorrhagic line at the periphery and is not undermined, ragged, or necrotic in uncomplicated cases.
7. The base tends to be clean, with a faint grayish pellicle, or a raw muscle color
8. The exudate is serous rather than purulent.
9. The chancre tends to be indolent and to run a slow course—three to eight weeks.
10. A painless, non-inflammatory discrete enlargement of the adjacent lymph-nodes, usually bilateral, develops after the first appearance of the lesion, and in about 70 per cent of the cases.
11. A notable exception to the bilateral character of the satellite adenopathy is the extragenital primary lesion, in which the adenopathy is usually unilateral.
12. On healing, a thin atrophic, often practically invisible, scar remains.

Long Incubation, Indolence, Slow Course and Satellite Adenopathy are the Outstanding Features of the Chancre in Diagnosis.

The Diagnosis of the Primary Lesion of Syphilis is a Laboratory Not a Physical or Morphologic, Problem.

The Evolution of the Chancre.—Formally speaking, the chancre is the first recognizable syphilitic lesion. It begins invariably at the point of inoculation. Morgan has shown that less than 50 000 organisms will not produce lesions in rabbits. Less than 1/150 cubic millimeter of chancre fluid will probably infect some persons. Shaw (1041) failed of infection after prophylaxis following a needle prick with chancre fluid (rabbit) containing 8 *Sp pallida* per oil immersion field. In theory the local reaction after a rather prolonged but somewhat indefinite period of incubation begins as a macule which develops into a papule. The accepted physical characteristics of the primary lesion are summarized in Fig. 210.

No one of these characteristics has independent weight, but derives all its significance from combinations with the others. For example while the single chancre is typical exceptions to the rule are now so commonly recognized that they have ceased to excite comment. As high as 20 chancres have

been reported in a single case (Almkvist) and 2 3 or 4 are common, especially where the infection begins in previously existent multiple lesions such as herpetic vesicles, scabetic burrows etc.

The chancre grows to size and conspicuousness dependent upon the virulence of the organism, the resistance of the tissues, the site and mode of inoculation, the degree of secondary infection, and the intensity of the local reaction. In size alone the chancre may vary from that of millet seed to an ulcerating tumor mass of 10 cm. in diameter or giant plaque involving the entire anterior aspect of the scrotum. The typical chancrous papule passes through series of clinical evolutionary stages corresponding to the tissue and general immunological reactions



Fig. 217 —A morphologically typical Hunterian chancre of the prepuce. The lesion is not chancre. The induration, base border and discharge were in every way characteristic. The lesion developed two weeks post coitus. It developed in tabetic with positive spinal fluid, though negative blood Wassermann reaction. (He thought himself immune.) Repeated darkfield examination was negative. The inguinal glands did not enlarge. The lesion was excised and the tissue examined by Dr A. S. Warthin for *Spirochaeta pallida*, with negative results. The histology of the lesion was that of simple inflammatory process This as not the sit of the original primary lesion so that it could not have been pseudochancre redux. The patient never developed further signs of re- or superinfection The case illustrates the fact that lesion may be typical chancre without being chancre.

described in Chapter I. A local edema followed by lymphocytic infiltration gives to the papule an unusual degree of shottiness and induration. Plasma cells are found in the infiltration, often in large numbers, and some fibroblastic proliferation occurs. The peripheral obliterative endarteritis results in superficial necrosis and destruction of epidermal surface which, at times, may be so marked as to give rise to definit slough. As rule, however an uncomplicated chancre is an eroded rather than an ulcerative lesion. This erosion in typical lesions yields serous exudate which on exposed surfaces forms thin, grayish-yellow slightly hemorrhagic crust (Fig. 8) The base of the erosion or ulcer is smooth. The border is usually regular and smooth, not raised, rolled, scalloped, or pearled. A distinct hemorrhagic or dark red line can sometimes be seen around the margin of the erosion. The lesion is usually relatively painless, but this most deceptive characteristic cannot be trusted at all. As the infection spreads locally from the site of reaction various

important concomitant phenomena, such as local lymphadenitis and sometimes lymphangitis, appear (Figs. 218, 219) With the progress of the local reaction, healing and fibrosis gradually set in. The epidermis rapidly regenerates over the erosion and healed plaque remains. The lymphocytic infiltration, which gives the plaque its induration, subsides much more slowly than the healing of the erosion and may remain for some time to mark the site of the active lesion. Spirochetes are present in the deeper portions of this infiltration and about the neighboring vessels, representing the remnants of the organisms largely destroyed by tissue reaction. The induration finally subsides, leaving no trace of the chancre, or there may remain at most only the most superficial and minute scar The impression that conspicuous scar means previous chancre is widespread error The uncomplicated chancre seldom leaves definitely recognizable scar in tissues which are naturally lax and flaccid. The accompaniments of the chancre in the form of satellite adenopathy and lymphangitis are important and are specially discussed below

The Hunterian or "Typical" Chancre.—While the expert, such as Fournier recognized and allowed for the tremendous variability of the primary lesion of syphilis, the verage physician has carried, from his text-book days, verbal photograph of the so-called "Hunterian chancre as his concept of the onset of syphilis. If lesion on the penis were solitary round or oval, had firm button-like cartilaginous indurated base convex eroded surface with raw-ham color



Fig. 218.—The bilateral discret inguinal adenopathy (satellite bubo) of the genital chancre The visibility of the nodes is increased by special lighting This young man was not ware that he had chancre or even genital lesion, and came for different complaint. The primary lesion is represented by thickening or sclerosis of the right margin of the prepuce, without erosion, ulceration, pain, discharge or other symptom. The lymph nodes are painless, firm, elastic, moderately enlarged and discrete. There as no secondary eruption, but the blood Wassermann reaction was positive. *Spirochaeta pallida* was present in the sclerosis.

thin serous discharge and hemorrhagic border not undermined, it passed as chancre with the verage observer (Fig. 217) If the lesion came on fourteen to twenty-one days after intercourse was painless, accompanied by discrete swelling of both chains of inguinal lymph nodes, the diagnosis was certain. But if one or two of the dozen or more variations possible were to occur, the lesion would be diagnosed chancroid, chaf hair cut, cold sore, etc. Experience with the late syphilis that follows misdiagnosed primary lesions and the masquerade under which its onset passed even critical inspection up to recent times, soon teach the comparative worthlessness of the purely clinical diagnosis of the chancre.

Syphilis without Chancre (Syphilis d emblée).—The new facts of great importance to the clinician which have come to light within recent years regarding the invariability with which a chancre will develop at the site of inoculation of *Spirochaeta pallida* (Fig 219) have been discussed from the immunological standpoint in Chapter I. So-called "syphilis d emblée" or syphilis without chancre has been a well recognized entity for a number of

years It was generally accepted however as the consequence of direct inoculation into the blood and was considered to be one of the rarest of syphilological accidents There exist quite definitely authenticated cases of puncture inoculation from needle pricks which appear to be true examples of syphilis d emblée On the other hand Almkvist in 1913 critically examined 23 reported



A



B



C

Fig 219 — An insignificant primary lesion of syphilis at the meatus. This patient was under observation following the finding of lat secondary eruption in his if (ho was infected from another source) Repeated examinations ere negative Six eeks after he was first seen the Wassermann, taken as matter of precaution, as returned positive Even with this guide his primary lesion was not discovered until the slight enlargement of the inguinal nodes, shown in A, was recognized. A the foreskin as dra n back the pipestem lymphangitis of the dorsal lymph channel was revealed (B) The slight pouting of the meatus (C) no more than ould have been produced by an irritating urine and totally thout induration, as then suspected, and on scraping the end of the intact penis the *Spirochaeta pallida* as recovered. The lesion was probably at this time about tw t three eeks old

cases of yphilis d emblée of which only 4 were accidental Needle-prick inoculations alone seemed to tand a searching analy is

The literature including articles by Lane Gottheil, Fordyce Hazen, and Feldman, consists largely of case reports in hich no particular distinction is drawn between hematogenous and local cutaneous inoculation. A critical analysis by Tièche subdivides syphilis d emblée into two types, hematogenou and lymphogenous, the former following blood transfusion (see p. 470)

The lymphogenous type may become manifest only in the form of inflammatory lymph nodes with an entire absence of visible primary lesions, though Tièche believes that minute initial sore may exist, unobserved by the patient. *A priori* there seems no intrinsic reason why the local tissue reaction to the organism need rise to the threshold of clinical recognition and experimental study has now shown that chancreless syphilis need not be even rare. Pollard reports what may well have been such case in a man who, although under close observation, apparently developed no more than *fugitive erythema at the meatus, followed at the usual interval by the appearance of secondaries.* This case is practically reduplicated by Fig. 219. Audrey and Chatelier have called attention to the complete change in the clinical onset of syphilis which may follow the engrafting of the spirochetal infection upon surface already ulcerative as result of some other type of primary infection. In cases of this type the only clinical manifestation may be the local lymphadenitis. This type of reaction is especially apt t occur in the mouth and throat, and furnishes highly perplexing clinical picture (see Fig. 248). Brown and Pearce have shown that inoculation upon the mucous membrane in the rabbit gives rise at times t practically imperceptible reactions, hich are none the less followed by general infection.



Fig. 220.—Indurated scar of chancre concealed in the pubic hair but identified after finding the satellite bubo. The lesion had developed at the lower angle of a fresh herniotomy scar and the patient was entirely unaware of its existence. He ppeared with florid secondaries.

While there can be no reasonable question of the existence of syphilis d emblée, and while it is a strong presumption that generalized syphilis may develop without a local reaction at the site of inoculation such cases should not discourage the clinician from making the most vigorous search into every out of-the-way corner of the body for the site of primary reaction to the infection in any given case. Every physician should be impressed with the fact that a chancre may assume almost any conceivable morphological form, and may occur on any accessible portion of the human body except the teeth, hair and nails.

Deceptive Incubation Periods.—The long incubation period ascribed to the chancre may be wholly deceptive in a negative way in that a short incubation may simply be that of a superposed banal infection such as a chancroid beneath which the chancre subsequently develops. Double infections with chancroid and syphilis thus appear not infrequently to have the short incubation of the chancroid but the long course of the chancre When the

base of a "chancroid" becomes clean and indurated a darkfield from serum aspirated from just beneath the lesion may show *Spirochaeta pallida*. Lesions whose incubation period is over ten days are definitely suspicious



Fig 221—Multiple chancres developing in the burrows of the itch mite (scabies). Darkfield positive



Fig 222.—A chancroid, so proved by negative spirochetal findings, positive Ducrey streptobacillus smear and negative follow-up for syphilis. There is a gangrenous type of chancre which may closely simulate this lesion.

Slow Healing and Prolonged Course.—Lesions which are the sites of syphilitic infection present, more often than any others, a combination of indolence with a prolonged course "It wouldn't heal" is the most common descriptive phrase obtained in naïve discussion from the patient. This con

trast between the mildness of the reaction and its long duration and obstinacy is, we believe one of the two characteristics of the chancre which



Fig. 223.—The pseudochancre redux, a gummatous recurrence at the site of the original chancre. No spirochetes can be found by darkfield, and there is seldom any associated enlargement of the adjacent lymph nodes. Note in this case the nodulo-ulcerative syphilid of the right wrist and the scattered nodules on the left.



Fig. 224.—A superficial ulcer of six weeks duration on the glans. The base was clean, the discharge serous or serosanguinous, the lesion only slightly tender There was bilateral inguinal adenopathy The border of the lesion was just sufficiently rolled to arouse suspicion, and a shaving removed from the edge before any attempt at darkfield examination showed the lesion to be squamous celled epithelioma. It had developed on a leukoplakial surface in a man of fifty years. Exposure other than marital was denied. The inguinal nodes were already involved.

has best withstood the revision of our clinical criteria by the more accurate and searching test of the darkfield

Induration.—Induration (Figs. 232 233) is the classical sign and makes the most impression on the beginner It involves the base of the lesion, results from edema and the packing of the tissues with lymphocytes and varies from the "visiting card" or parchment induration, barely palpable by the expert and the cartilaginous button slightly larger than the base of the ulcer to the brawny wooden induration of the giant chancre of the lip (Fig 225) or the rubber-ball induration of the phymotic chancrous infiltration of the redundant foreskin. Spurious or factitial induration not due to syphilitic infection has long been recognized and is likely to be confusing in lesions which have been subjected to irritative treatment, especially with chemicals or the actual cautery In a lesion which has been subjected to such treatment, induration is without clinical significance and must be absolutely dismissed for the time being from the list of criteria

Erosion vs Ulcer—It is more characteristic of the other infections with which the chancre may be confused, such as chancroid (Fig 222) infected herpes progenitalis, treated erosions, secondary pyogenic infections, gum



Fig. 225 —The giant chancre of the lip brawny wooden, phlegmonous induration with marginal ulceration. (Collection of F G Harris.)

matous recurrences (pseudochancre redux—Fig 223) and malignant lesions, that they produce not erosions, but ulcers (Fig 224) On the other hand, this criterion has now been shown so many times to be common to insignificant lesions, and lacking in what subsequently prove to be true chancres, that no attention can be paid to it.

The Border—In the typical chancre the border is flat not elevated or rolled and the transition from the slightly convex surface of the erosion is at times almost imperceptible A frequently observed feature is the slightly hemorrhagic line of dilated capillaries (Fig 220—new formation of capillaries) about the margin of the erosion Undermined borders suggest secondary infection of the chancre or that the lesion is a chancroid phagedena or tuberculosis. The border has relatively little weight in differential diagnosis in the light of modern knowledge

The Base—A typically indolent chancre usually has a clean base A thin grayish pellicle forms if it is moist or protected (see Figs. 232 and 237) Where the lesion occurs on the exposed skin a crust usually forms but this on removal shows a relatively smooth base (see Fig 217) Secondarily infected and

true chancroidal ulcers are much more apt to be rough dirty and necrotic, and covered with purulent exudate (Fig 222) On the other hand it is entirely possible for the chancre to have a necrotic base and clinical lesions resembling



Fig. 226.—A false induration developing in lesion about the fourth week after the frenum had been destroyed by the ulcer Not the clean base and hemorrhagic border suggesting chancre developing on the base of chancroid. The lesion was proved nonsyphilitic by repeated darkfield examination, aspiration of the base, and four months of observation and Wassermann follow-up.



Fig 227 —The remnant of the glans penis following gangrenous balanitis. The corpora cavernosa had sloughed away over the end of the penis to their ttachment at the crura. This patient, sixty-three years of ge also had syphilis, but it was probably a lat infection rather than coincidence of primary lesion and gangrenous balanitis.

chancres with necrotic bases but showing no signs of being syphilitic have been ecognized.

Phagedenic Genital Lesions.—Necrosis is the characteristic *par excellence* of the group of lesions included under the term "phagedena and gangrenous balanitis (Fig. 227). In the latter

condition especially which is an infection with Vincent symbiosis of large spirochete and fusiform bacillus, gangrene may be wholesale and take place with terrifying rapidity amputating the genitalia (Fig 227) or involving the corpora cavernosa of the penis from the glans to their insertion into the pubes. For some reason the glans and the corpus spongiosum have been relatively resistant in the cases we have seen. It is rare but not impossible for syphilitic infection to be engrafted upon lesion of this sort.

Satellite Bubo —The lymphadenitis (Figs 218, 219 228, 230) associated with the development of the chancre is one of its most constant and characteristic features With the indolence and slow course, and to a less extent the induration, it has *survived the critique of darkfield practice and stands* today as one of the most unvarying and trustworthy of the few remaining clinical guideposts in the recognition of the disease. Fournier rated it as without question the most valuable sign of the chancre, and begins an entire chapter devoted to its consideration by the vivid words of his preceptor Ricord "Il est le compagnon fidèle du chancre il l escorte invariablement, fatalment il suit le chancre comme l ombre suit le corps. Pas de chancre infectant, sans bubon, voila ce qu on peut donner hardiment comme une loi pathologique. Exceptions, however are not so rare as the purely clinical evidence would suggest Approximately 30 to 40 per cent of primary lesions in our experience at the time the chancre was identified by laboratory evidence, did not present a clinically significant associated local adenopathy Even with this qualification the "satellite bubo" remains an extremely important suspicion arouser "

The satellite bubo almost invariably involves the nearest group of lymph nodes to the lesion. One of the occasional exceptions in our experience has been the escape of the epitrochlear node in chancres below the elbow and the appearance of the bubo in the axilla, a point to be borne in mind in lesions on the fingers. The adenitis like the chancre is characteristically indolent in uncomplicated cases, though benign secondary infection and the Ducrey streptobacillus may as secondary invaders, altogether alter its course. Enlargement of the nodes seldom begins before the seventh day of the life of the primary lesion, so that it has little diagnostic value in the very period when the chancre most needs to be recognized and yet offers the least to make its clinical identification possible The recognition of chancres by darkfield examination before the fifth to the seventh day of course, anticipates the presence of an adenopathy The involvement is usually bilateral in lesions about the genitalia, and unilateral elsewhere, even in lesions near the median line The process about the genitalia involves a whole chain of nodes rather than a single node and this pleiade" or chain was rated by the French syphilographers as one of the most characteristic features of the chancrous bubo The individual nodes are usually discrete firm but not hard move freely beneath the skin, show no signs of inflammatory character in the form of matting with other nodes or erythema of the surrounding skin, and are practically painless. Secondary in vasion at once modifies the entire picture and softening or suppuration may then take place. We have been unable to confirm from our own experience Fournier s statement that the satellite bubo in lesions in the mouth and about the neck is especially apt to show periadenitis with softening and a tendency to suppuration We have never seen a suppurating cervical satellite bubo even under conditions most favorable to infection. Lymphangitis of an indolent sort is occasionally observed especially in some chancres of the penis, in which the central dorsal lymph channel exhibits a

marked degree of involvement usually spoken of as "pipestem lymphangitis (Fig 219)

Adenopathy in Malignancy—The time element in the development and course of the local adenitis is especially important in the differential diagnosis of malignancy (Figs. 237 238) The satellite bubo appears earlier in general than the adenopathy of metastatic malignancy the former developing in the first to second week, and reaching the maximum usually by the third or fourth week; the latter not being present t all at outset unless marked secondary infection occurs, and only appearing after lapse usually of several months. The dangers of attempting differential diagnosis on this basis, however become so pparent as one clinical experience grows, that it is safer to resort to darkfield and tissue study than to waste time in arguments about so uncertain distinction.

Local Adenopathy as Guide to the Location of Healed Chancre—One feature in the chronology of the bubo is of much importance, however This is its persistence beyond the time of beginning healing of the chancre It may last for eeks or months, and in the case of more than one patient with an unrecognized or healed primary lesion and evidence of fully developed recent infection, it may serve as guide to the region in which the chancre developed and lead to the identification of its scar (Fig 240)



Fig. 223.—The unilateral satellite bubo (below the left ramus) in chancre of the upper lip.

Variations in Local Adenopathy—The satellite bubo, apart from its variations under conditions of intercurrent infection and treatment of lesions, presents intrinsic variations ranging from complete absence to giant tumefaction suggesting Hodgkin s or malignant lymphoma. Fournier is authority for the statement that there are no important variations in the two sexes There seems to be no necessary relation between the size or character of the primary lesion and the size of the satellite bubo under ordinary conditions of inoculation. The group of cases reported by Audrey and Chatelier under the title "Bubon d emblée, syphilis cryptocarcinique" furnishes an important variation on this statement These authors report five cases in which, under the clinical appearance of malignancy of the tonsil and pharynx, enormous satellite adenopathies developed which from the subsequent course of the cases proved to be the satellite bubos of extragenital syphilitic infections which did not develop anything to suggest typical chancres. In this connection it is very important to recall the possible errors in pathologic diagnosis which may be made in studying sections from lymphomas when the possibility of

syphilis is not borne in mind. Moore calls attention to the increased tendency of Negroes to lymphoid reaction, including satellite bubo as compared with whites



Fig. 229.—A solitary gland of tuberculous origin. Note the tuberculid of the ear (moth-eaten ear) which identifies the process as tuberculous.





Fig. 230.—Tuberculous (not syphilitic) primary lesions in the temporal region, and cheek, A with its metastatic satellite lymph node. The satellite adenopathy of a tuberculous "chancre" may be found at a considerable distance from the inoculation site. On the genitalia, and about the mouth the syphilitic and the tuberculous chancre may so closely resemble each other as to be confused. As a rule the tuberculous chancre is much slower in developing and the apple-jelly tubercles often present can be recognized under glass pressure in the inflammatory areola, even though they may not be distinctly visible above. The tuberculous node tends to break down, the syphilitic satellite bubo does not.

The differential diagnosis of the satellite bubo in the groin is relatively of little importance to modern practice. It is impossible to distinguish chancre and chancroid by this means. Its absence in pseudochancre redux may be of

assistance in diagnosis, but it becomes highly significant in lesions about the head neck, extremities, and nipples About the head in particular it is usually unilateral (Fig 228) Vincent's angina in the throat may give rise to unilateral adenopathy often rather marked. But it is very much safer to investigate such cases thoroughly for syphilis than to fall into the very common interpretative errors represented by such cases as Fig 255

The adenopathy of inoculation tuberculosis is slower to develop (Figs. 230A, 231) more chronic, except in so-called "tuberculous chancre" or primary inoculation tuberculosis, usually marked by periadenitis and often associated with suppuration which is rare with the satellite



Fig 231—A tuberculous "pipestem lymphangitis" associated with a tuberculous primary lesion on the forearm and a satellite bubo in the axilla.

bubo (Fig. 231) If the lingual, tonsillar and pharyngeal lesions of the malignant lymphomas have an associated unilateral adenopathy it is much the safest course to investigate the possibility of syphilis by gland aspiration, Wassermann test, and complete examination, after prolonged observation, even though a pathologic study of these may have seemed to confirm the diagnosis of lymphoma. The possibility of gummatous adenitis must be borne in mind, though the condition resembles tuberculosis more than the satellite bubo (Fig 860)

Common Variations in the Chancre.—The chancre on the male genitalia assumes, more often than anywhere else the typical Hunterian form. On the glans there is nothing especially distinctive about its course, unless it develops at the meatus, in which case it may involve one or both lips, is usually of refractory type due to the irritation to which it is subject, and is said by

Fournier to run an especially chronic course which is hardly true under modern treatment Care must be taken not to pass too lightly over the edema of the *meatus often associated with gonorrhea, since this may be in fact an initial* lesion (see also Fig 219) The frequency of this association has been confirmed by the observations of Shropshear and Hibbs Palpation of the meatal as well as the urethral chancre should be in the long axis of the penis as well as transversely across the plaque The former manipulation may be the only means of detecting induration

Preputial Chancre.—The chancre of the anterior margin of the corona has no distinctive characteristics That of the posterior or preputial border of the corona, however (Fig 234) exhibits induration to the best possible effect. On retraction of the foreskin a saucer or boat-shaped cartilaginous plaque



Fig. 232.—A slightly scaling papule with faint induration—all there was to this patient's chancre Such lesions, if they attract the patient's attention at all, are interpreted as chafes, "hair cuts," etc. The induration is barely perceptible Such lesions may also follow the application of irritants to slight abrasions.



Fig. 233.—Massive induration of the frenum and glans penis in chancre at the sulcus coronarius.

suddenly flops back much as the tarsus of the upper eyelid flops back from the surface of the eyeball under the hand of a skilled ophthalmologist. We had always felt this particular "dory flop" induration to be almost as diagnostic as a positive darkfield until we encountered the case shown in Fig 235

Chancre of the frenum and of the lateral folds of the prepuce is especially apt to escape observation One of us (J H S) has seen the frenum all but amputated with the patient barely aware that anything was the matter The lesions are often small mere erosions, rather than indurated papules.

Phymotic Chancres.—The phymotic chancre is a not uncommon variety and is often confused with the balanoposthitis that may accompany a severe gonorrhea. It should always be painstakingly investigated for evidence of syphilis. Three types are recognized the doughy infiltration of the foreskin en masse nodular multiple infiltrates (Fig 233) and the rubber-ball type of

diffuse infiltration resulting in a firm ball-like enlargement of the prepuce and glans Not a few of these phymotic lesions are subjected to dorsal slit operations with risk of phagedena when a thorough examination of the discharge for spirochetes and the prompt institution of treatment would make such a mutilation unnecessary It is highly important in this type of lesion to avoid paraphymosis by attempted retraction of the foreskin in mild cases In the diffuse type and in cases with a chancre at the preputial edge cicatricial contraction of the opening in the foreskin may be marked and necessitate later circumcision when the process is healed



Fig 234 —Highly characteristic induration of the prepuce (double chancre). Compare Fig. 235. On drawing back the foreskin, this induration "flops back in almost diagnostic fashion.



Fig. 235 —Highly characteristic induration of the prepuce. This is not chancre but an induration produced by an infected sebaceous cyst. On aspiration pus as obtained, and pus as obtained from the enlarged inguinal nodes A complete follow-up demonstrated that the patient did not have syphilis. Note the "Fordyce disease of the glans (hypertrophied mucous glans).

Urethral Chancre.—The endourethral chancre is relatively rare, or at least seldom comes to clinical recognition.

The most recent studies indicat that the rarity is more apparent than real, and is due to the masquerade of this type of lesion under the symptomatology of gonorrhea and nonspecific urethritis. Friedman and Maner (1936) pointed out that in patients with gonorrhea but no penile lesions, persistent urethral discharge, examined by darkfield, may disclose an endourethral chancre. By special method for the darkfield examination of gonorrheal pus, Friedman (1939) identified *Sp. pallida* in the discharge of acute gonorrhea in 2 of 40 cases. Shropshear and Hibbs (1941) observed 10.7 per cent of primary and secondary syphilis in patients with gonorrhea, and 14.2 per cent of their patients with primary syphilis had coincident gonorrhea. In their series nearly one-third of the cases ith primary syphilis and coincident gonorrhea had intrameatal primary lesions A blood-tinged seropurulent discharge associated with redness and induration of the meatus or urethra with satellite adenopathy is, in their opinion, highly suspicious. Curley (1937) emphasizes the necessity for palpating the urethra in the male and examining the vagina,

cervix and urethra of the female for localized swelling with darkfield examination of the discharge Kemp and Shaw (1936) found that 26 4 per cent of 153 syphilitics in 1000 cases of acute gonorrhea had contracted their syphilis simultaneously with the gonorrheal infection. In every instance in which primary syphilis was present, it was diagnosable without dependence on the positive blood serologic tests. Army observers (Loveman and Morrow) emphasize the frequency of endourethral chancre in patients studied for gonorrhea who have coincident enlarged inguinal lymph nodes suspected of being lymphogranuloma venereum. Careful palpation will often disclose the site of the primary lesion, and darkfield examination of the lymph nodes reveals spirochets conforming to the type of the somewhat thickened organism which is within the range of morphologic variation for *Sp. pallida*.

It seems, also from general statistical estimates of the proportion of syphilitic infections which have presumably a masked onset (only a history of gonorrhea obtainable) that mild cases of seeming gonorrhea, and cases in which after a short acute course a thin serosanguineous discharge persists



Fig 226.—Very early epithelioma at the frenum, producing an erosion and slight induration, studded with minute translucent pearly nodules. Tuberculous lesions at the meatus may also occasionally be deceptive

would by a more systematic darkfielding and clinical study be shown to have their origin in urethral primary lesions. Certainly the 10 per cent of patients with syphilis who can give no history except that of gonorrhea represent a sufficiently large proportion to justify a Wassermann follow-up of every patient with gonorrhea and further study by darkfield if the gonorrhea runs an atypical mild course

The Genital Chancre in Women.—Genital lesions in women have been the subject of many conflicting statements due in part to the fact that in the casual management of patients they are both relatively inaccessible and therefore not seen and the victims of them are relatively uninitiated and uninquiring The problem of recognizing primary syphilis in the woman, therefore differs sharply and greatly to the detriment of the public health from that of identifying primary infection in the man The conflicting conceptions of the subject, dating back, many of them to predarkfield days have been thor

oughly modernized by the work of Gellhorn, Stookey and MacDonald in this country, and by the remarkable monograph of Anwyl-Davies from Great Britain which records and analyzes the largest existing experience. An extensive literature has recently been reviewed by Pariser (1941–1942) in connection with the *problems of the transmission of syphilis* by the woman. The conspicuous fact, brought forward by recent investigations, is the large proportion of primary infections which takes place on the cervix uteri.

Fournier's figures in 1906 reported 45.6 per cent of chancres in women on the labia majora and 22 per cent on the labia minora, with only 5.2 per cent on the cervix. The studies of Anwyl-Davies, however, show that the incidence of cervical chancres is 44 per cent in a series of 512 cases of primary syphilis, while the labia majora stand second with 31.3 per cent. Chancres of the labia minora, fourchette, urethra, and clitoris range from 8 to 2.7 per cent, and chancres of the vagina, vestibule, perineum, mons veneris and adjacent structures are among the rarities ranging from 1.4 to 3 per cent.

The morphology of the chancre in women varies markedly with the location of the lesion, and the lesions in general present variations on the erosive, the ulcerative, the papular and the indurative type, the induration being circumscribed or diffusely edematous. The differences between the primary lesions on the external genitalia in the man and the woman appear to have been overemphasized by the literature in the past, there being, apparently, few fundamental differences except those associated with distribution. Chancre of the clitoris is a comparative rarity in the woman, of course, in contrast to chancre of the penis. *Chancre of the urethral orifice, usually annular, is frequently mistaken for carcinoma.* Chancre of the vagina, on which Bille has collected the literature, is a rarity due, according to Pariser and others, to the low pH of the vagina and the lack of glandular openings. Syphilis d'emblée in women is an established fact, Anwyl-Davies reporting cases with a normal external os in which *Spirochaeta pallida* was obtained from the clear secretion from the canal. Pariser cites a number of observers, including Fuchs, Trost, Lesser, Puente and Gellhorn, who have identified *Sp. pallida* on the normal cervix after contact with infected individuals. It is also possible for *Sp. pallida* to be present on the cervix if a syphilitic primary lesion is present on the external genitalia, Gaucher recording a series of cases in which, if a primary lesion existed at all, it must have involved the endometrium. Warthin believed that nonformation of a chancre is particularly likely to occur where the organism penetrates a columnar-celled mucosa. In one case of primary syphilis of the endometrium he found that the perivascular infiltration had extended along the blood vessels, through the uterine wall, even into the broad ligament. Much too little attention is paid by the older observers to the confusion possibilities in the morphology of spirochetes present about the female genitalia particularly. This subject is adequately reviewed by Pariser. Further research will be necessary to establish the real significance of morphologic confusion of organisms obtained from the intact genital structures of women. In most instances where *Sp. pallida* indubitably is present, critical examination of the cervix will disclose an endocervical lesion or an involvement of the endometrium by a primary, secondary, or recurrent infectious process.

The Cervical Chancre.—The pseudorarity of the lesion is almost certainly the product of nonrecognition and of failure to use the speculum examination or to keep syphilis in mind as a possibility while making it. The cervical chancre is centrally placed, that is, surrounding the external os in 92 per cent

appears on the posterior lip in 17.5 per cent and on the anterior lip in only 9.5 per cent It is generally in the type encircling the os, somewhat larger than the male genital chancre but may vary from a large tumid induration to a mere macule, or in Anwyl Davies case to a pinhead-sized herpetiform vesicle

Th types of cervical chancre include the erosive, the ulcerative, and the diffuse indurative type which is relatively common and which has passed largely unrecognized except by Stookey and by Anwyl-Davies. Stookey also mentions the classical Hunterian lesion and two diphtheroid chancres. Anwyl-Davies, who has watched the development of the primary lesion following exposure in number of cases, states that the chancre begins as an erosion, generally single and central, surrounding or touching the external os at some points. The erosion is circular or oval, occasionally irregularly contoured, well defined, sharply circumscribed, regular in outline and with sloping edge. The ulcerative type, one third as common as the erosive, may extend to large fungating hypertrophic ulceration covering the whole cervical surface. Warthin believes that this type is the product of the invasion of the organism through squamous cell epithelium. Stookey believes that the diffuse indurative type is the most common chancre of the cervix, but Anwyl-Davies rates it as less frequent than the two previous types. Stookey and Polsky (1936) have called attention to what they describe as cold edema of the cervix, which is in reality diffuse indurative primary lesion without inflammatory or erosive characteristics. The size of the cervix is greatly increased and the consistency of the whole tissue assumes an India-rubber character elastic and indurated. N erosions or ulcerations can be detected and the diagnosis is confirmed by the presence of *Spirochaeta pallida* under darkfield examination in the secretions from the cervical canal. Simon (1938) states that the satellite bubo of the chancre of the internal genitalia in women can be palpated in the vaginal fornix over the external iliac vein

In the pregnant woman the primary lesion on account of increased vascularity of the pelvic tissues, is larger more conspicuous and generally indurated. On the cervix there may be extensive erosion and fissuring and a rigid, unyielding scar which interferes with dilatation of the cervix may result, a number of cases having been reported in the literature.

Malignant disease of the cervix is more frequently confused with chancre and gumma of the cervix than with any other disease The fugitive character of the syphilitic cervical primary lesion, formerly emphasized in the literature, has been discounted by Stookey and other observers and gynecologists no doubt see a number of chancres a year under the disguise of cervical erosions, vegetative lesions suggesting carcinomas, and the like The differential diagnosis of these lesions is extensively discussed by Anwyl Davies, to whose monograph reference should be made. Warthin was so impressed with synchronous carcinomatous and primary syphilitic involvement of the cervix that he insisted on biopsy even if *Sp pallida* was present.

The recognition of the primary lesion in the woman is then a matter of vigilance and routine search rather than of intrinsic difficulty Speculum examination should be made of the sexual partners of all male patients who are known to be in the infectious period of the disease The lack of routine speculum examination by an experienced observer accustomed to the tremendous range of variation of the primary lesion in women invalidates as statistical evidence some of the numerically large series in the literature In this way the inevitably high percentage of women who escape early recognition of their infections can be at least to some extent, reduced The very great importance of systematic examination of the cervix for all types of early syphilitic lesions has been clearly brought out by MacDonald who in an examination of 233 women found 91 with so-called "cervical erosions" with positive darkfields in 9 0 per cent, and 14 2 per cent who in addition had a positive Wassermann reaction with a negative darkfield. In their series of 233

erosions, 42.5 per cent of the lesions turned out to be syphilitic, in 60 per cent the diagnosis being established by the darkfield and 81.8 per cent by the positive serological test. It is evident, therefore, that darkfield equipment is as essential in the office of the gynecologist as in that of the syphilologist.

THE EXTRAGENITAL CHANCRE

The primary lesion of syphilis when it develops on other parts of the body than the genitalia, is protected from recognition by a singularly low threshold of suspicion on the part of physicians. A lesion on the genitalia may arouse some suspicion *a priori* but a lesion on the finger the lip, or the tonsil seldom does Syphilis seems to be suggested last to the examiner instead of first of all the existing possibilities. As long as this state of mind exists the recognition and proper appraisal of extragenital onset in this disease will be anything but complete.

Chancre of the Lip.—The overwhelming proportion of extragenital lesions occur about the mouth, as might be expected when the popularity of mouth to-mouth contacts and the predilection of infectious lesions for this site is considered

In Bulkley' monumental compilation, 20 per cent of extragenital chancres occur upon the lip, probably due to the fact that the literature he reviewed emphasized other rarer types of lesions. In his private cases 65 per cent occurred about the mouth. Fournier found 75 per cent occurring about the head, and of these, 66 per cent upon the lips. Cole (1916) found 77 per cent of the extragenital lesions observed by him occurring on the lips. Tobias (1936) found the proportion on the upper as compared with the lower lip, as 20 is to 16. Wile and Holman (1941) found 46 per cent lip, 10 per cent tonsil, 6 per cent finger 5 per cent tongue, 2 per cent breast, 2 per cent pharynx, 1.5 per cent each of forehead, chin and arm.

Extragenital Infection in Children.—Waugh (1936) in small series between five months and eleven years of age, found only tw who had acquired syphilis through definite sexual contact. Smith (1930) pointed out the relatively small number reported of many cases collectable, the preponderance of females, the importance of household contacts, the importance of sporadic family epidemics in which an adult or older child, acquiring the infection by sexual exposure, transmits it extragenitally to others. Sleeping with person ith secondary syphilis was the means of transmission in eight cases. Extragenital chancres are frequent, 90 per cent of them occurring about the face and neck. Smith identified also cases of transfusion syphilis alone in his series. Applebaum (1937) reports chancre of the upper eyelid in an infant two months of age which he believes to have been acquired from the birth canal of the mother who had late secondary syphilis

Kissing.—This constitutes apparently the overwhelmingly predominant mode of transmitting the disease extragenitally Chancres from genitobuccal contact are comparatively rare, so that the real danger lies in the ordinary osculatory salute and the "baiser d'amour " There are few things more dangerous than being kissed by a syphilitic, and all patients with the disease should be strictly and specifically enjoined against the practice.

Certain occupations have in the past been subject to special risks of mediate mouth transmission and epidemics of syphilis among glassblowers, for example, have occurred. The common drinking cup in a gang of men may be a prolific source of infection and the same principle applies to all utensils and tools which may convey material from the infected mouth to suitable sites on the body of the victim. Droplet material from coughing or spitting is a real danger likewise. The chancre of the lip that follows the familiarities of an engagement in which either party but more often the man, has active lesions in the mouth is more common than is realized.

The surprising turn which such infections may tak is suggested by Shaffner' report of chancre of the eyelid in woman following a daughter ttempt to remove a foreign body from the mother eye with her tongue In Schamberg famous case 7 young women developed primary lesions of syphilis following kissing game in which a young man participant had hancre of the lip. Another young man was subsequently infected by kissing one of the infected girls.



A

B

C

Fig 237 —Chancre of the upper and lower lip, and epithelioma of the lower lip in young man of twenty-six A, with chancre of the upper l p as brought to the clinic to have the tumor excised. B shows the edematous border of chancre which may sometimes suggest malignancy C shows the rough base rugged edge nd "pearling of the border in an epithelioma.

Differential Diagnosis of Lip Chancre.—Chancre of the lip should therefore on account of its frequency form part of the routine mental differentiation applied to every lesion of the lip at its first examination (Fig. 237) It is as true of chancre of the lip as of the primary sore upon the genitalia, that every single *one of the criteria of purely physical diagnosis may fail to identify the lesion*

as syphilitic. For this reason the attitude of mind that a lesion upon the lip is a chancre until it is proved otherwise is the safest from the standpoint of the recognition of syphilis, though too sweeping for general acceptance. Certainly any lesion which presents the group of three characteristics mentioned as still surviving the critique of darkfield study should arouse suspicion. A lesion which is indurated slow to develop and heal, and associated with a marked satellite adenopathy is a chancre until it is proved otherwise

Differentiation of Chancre and Carcinoma About the Mouth.—This pronouncement brings us face to face with a possibility more frequent and serious about the mouth than upon the genitalia Squamous cell epithelioma (Fig. 238) developing upon normal mucous membrane, upon a previous leukoplakial patch or upon an actual gumma may simulate chancre to the minutest detail Delay in the diagnosis of epithelioma of the high grade of malignancy usually encountered about the mouth and lip is more serious than delay in the diag-



Fig. 238.—Epithelioma of the lip in patient with positive blood Wassermann reaction and cutis marmorata that was confused with secondary eruption. Note the easy bleeding of the lesion and the leukoplakia at the left commissure. There is satellite bubo (malignant) below the ramus of the jaw to complete the resemblance to chancre (see text)

nosis of a chancre in the same situation For that reason it is unpardonable to use time-consuming procedures like the serologic follow up as the sole resort in the differentiation of malignancy about the mouth from chancre A diagnosis can however be clinched forthwith by the procedure employed in Fig 238

In this case darkfield examination of the lesion was made first. A Wassermann examination taken at the same time was positive The darkfield was negative as might be expected in late chancre, and the Wassermann on repetition was again positive. Even this combination of evidence does not prove the patient to have chancre. Treatment was at once instituted and three arsphenamine injections in five days failed materially to alter the appearance of the lesion. A piece of tissue was then removed for frozen section diagnosis, with the patient prepared for operation, and report of squamous cell epithelioma returned

The correct diagnosis had however been predicted from a single detail of examination which assists in raising a suspicion of malignancy about the lip The typical chancre of the lip bleeds very little even on rather rough

handling The epithelioma, on the other hand usually bleeds on the slightest touch The slight distortion of the lip in photographing the lesion in question (Fig 238) resulted in pronounced bleeding The pearly border of epithelioma, composed of hard slightly translucent nodules each with its little rim of dilated capillaries visible under the lens, is of material assistance in identifying many malignant lesions. It is not, however invariably present and, as shown in Fig 237 B an inflammatory flange-like edge on a chancre may give a momentarily false impression If the suspicion of epithelioma is strong as little manipulation as possible should be employed in studying the lesion and serum for darkfield examination should be collected without scraping or squeezing It may be preferable in reaching a diagnosis to perform a biopsy first and examine the shaving of tissue by frozen section with the patient prepared for operation in order that no dissemination of the carcinoma may result if the pathologic findings are positive.

Cole in his study of the extragenital lesion directs attention to the value of the inflammatory quality of the chancre in differentiating it from other lesions about the lip This is especially useful in leading to the fuller investi-



Fig. 239 —A gumma of the upper lip simulating chancre, but treated for some time with silver nitrat On involution under treatment for syphilis scarcely scar was left.

gation of supposed epithelioma which is relatively noninflammatory It is not, of course proposed as an absolute criterion.

Wile and Holman (1941) observed the healing of chancre under radium (which might further the confusion with carcinoma) and have seen treatment-resistant primary lesion finally healed by roentgen-ray (Beerman, Ingraham and Parker 1943, case of Hough a.)

Further Differential Diagnosis of Lip Lesions.—The further objective differentiation of lesions on the lip includes gumma, pseudochancre redux, inoculation tuberculosis, sarcoid vegetative dermatitis pyogenic granuloma chancroid blastomycosis, and sporotrichosis.

Gumma (Fig 239) is usually identified by the slower course, absence of satellite adenopathy and negative darkfield examination. The histopathologic findings and Wassermann, of course may not be distinctive (see Chapter I). Pseudochancre redux is identified by the same criteria. Inoculation tuberculosis rarely occurs on the lip, although this may be the origin of so-called "tuberculosis orificialis faciei, from secondary involvement of the throat and nasopharynx. The apple-jelly nodule small, translucent, brownish tubercle recognized on blanching the erythematous surface by glass pressure is usually easily identified. The satellite adenopathy of inoculation lesions usually suppurates early and tubercle bacilli can often be found in the discharge (Fig 240). Sarcoids, rarely seen about the lip, but often around the nose and cheek, are tumors or plaques,

of tuberculoid histologic architecture which practically never ulcerate or erode. They are negative to all examinations for syphilis, but may respond to arsphenamine treatment, though not so readily as syphilis. Vegetative dermatitis usually presents the mammillated surface and pus crypts of the pyogenic granuloma, but may at times, on the lip, form the sessile or pedicled dark red, easily bleeding tumor now known to be merely a highly vascular granuloma of pyogenic origin. These lesions are negative to darkfield and other examinations for syphilis and clinically are not very suggestive. Chancroid of the lip is excessively rare and presents the same general features as on the genitalia. The earmark of blastomycosis, which is also rare on the upper lip, is the extending papillomatous border with central contractile scar and the minute epithelial abscess, found between the papillomatous projections of the margin. On pressure with a ring curet over the margin several minute droplets of pus can usually be made to exude. In this pus the blastomycete may be found, a typical yeast with double refractile wall and budding forms. The diagnosis should not be attempted by the inexperienced on microscopical grounds alone. Sporotrichosis of the upper lip produces a small pustule which extends, giving rise to early metastasis to adjacent lymph nodes and the skin along the connecting lymphatic channel. It is well to take cultures on lesions of the lip if they are infected or ulcerated. Maltose agar and room temperature are necessary for the growth of sporothrix.



Fig. 240.—Fissured chancre at the labial commissure, with submaxillary adenopathy.

On one occasion an infected hemolymphangiomatous nodule produced a picture on the upper lip requiring differentiation from chancre. A cluster of minute lymphangiomatous vesicles could be recognized on the border. The tularemic "chancre" may too, as presently discussed for the finger, conceivably require differentiation on or near the lip.

Herpes of the lip deserves special mention in differentiation because while the cluster of vesicles with their polycyclic or scalloped confluent borders and superficial crusting is generally easily recognized, herpes is the commonest misdiagnosis of early chancre of the lip. A herpes which requires more than two weeks for its involution is suspect, especially if any signs of associated unilateral adenopathy have appeared. A more determined policy with reference to the darkfield search of such lesions would doubtless result in many negative findings, but would arrest at its onset many a tragic case of extragenital syphilis, especially in the young fiancée.

Oral and Pharyngeal Chancres.—The chancre within the mouth and pharynx is much less common than upon the lips according to the Fournier

statistics (3 lip to 1 mouth chancre) Here again a wide range of variability is possible, while the difficulties of exact laboratory diagnosis are unfortunately markedly increased by the unreliability of darkfield findings in the mouth and throat. An inconspicuous type of chancre of the tongue is the smooth eroded plaque whose induration is best apparent on palpation (Fig 241) and which is almost devoid of subjective symptoms The ulcerative type described by Fournier is much less common

Tw rare types, the fissured chancre and the diffuse plastic infiltration, are also described. The former is t times difficult of distinction from the fissured tuberculous lesion of the tongue, and the latter may be confused with diffuse gummatous infiltration and epithelioma. W have seen tuberculosis, with the bacilli present in the lesion nd in the sputum, mimic almost perfectly the fissured and the eroded plaque types of chancre of the tongue. The discovery of signs of pulmonary tuberculosis t first examination, and smear stained by the Ziehl-Neelsen technic usually identifies the tuberculous element, but should not discourage full investigation for the possibility of syphilis Clinical identification of t berculosis does not exclude the possibility of syphilis.



Fig 241 —Chancre of the tongue, showing merely slight erosion. The induration, however as pronounced. On deep aspiration of the base the *Spirochaeta pallida* was obtained

Chancre of the gum is regarded as a rarity and in all probability this rarity is genuine and not the product of lack of recognition.

The simple erosive type ill probably arouse suspicion of itself but the diffuse form, described by Fournier *alveolodental periostitis, of which Fig 260 was perhaps an example* is probably seldom identified as such. Klauder has described case with study of the literature.
Through the courtesy of Professor Wile, one of us (J. H. S.) has also had the opportunity to see gingivitis involving the right side of the lower jaw from which *Spirochaeta microdentium* was obtained in almost pure culture The organism in darkfield is difficult to distinguish at times from *Spirochaeta pallida* and might have produced deceptive impression of early chancre of the gum.

Chancre of the Tonsil.—The tonsillar chancre is, in our opinion the most neglected from the standpoint of early diagnosis of all the buccopharyngeal primary lesions Morton Smith has hazarded the opinion that it is really very common, and there can be no doubt that it frequently masquerades as diphtheria Vincent's angina, carcinoma and lymphosarcoma of the tonsil While bubo is known to be a feature of Vincent's angina, there can be no question that such cases deserve painstaking study for syphilis and an appropriate

follow-up and observation instead of the local treatment followed by tonsillectomy and dismissal which is too often the rule.

Simple chancre of the tonsil is almost invariably *unilateral*, and appears as a firm, slightly elevated plaque, at times with surprisingly little involvement of the peritonsillar tissues. The surface covered with a grayish exudate, is at times difficult to distinguish from the tonsillar mucous patch. The degree of induration is very variable and according to Fournier may be altogether absent. The detection of the induration is made difficult by the inaccessibility of the lesion, but with practice the tonsil can be propped against the posterior pillar with a flat wooden tongue blade and the degree of induration tested by pressing the base of the tonsil with the end of the blade.

Crateriform ulceration of the tonsillar chancre may occur and, with the induration and eversion of the border may simulate carcinoma. The age of the patient while suggestive does not by any means settle the question now that a more trustworthy criterion is available in laboratory diagnosis.

Differential Diagnosis of Tonsillar Chancre.—Diphtheria, Vincent's angina, and lymphosarcoma are the most difficult lesions to differentiate from chancre of the tonsil. Clinically the chancre may simulate even the adherent membrane of diphtheria and the gangrenous extensions on to the pillars and palate with associated lymph node enlargement seen in Vincent's angina.

The identification of Vincent symbiosis of large spirilla and fusiform bacilli in smears does not by any means prove the condition to be an uncomplicated Vincent's angina. Many ulcerative mouth lesions, including both undoubted malignancy and undoubted syphilis, may be contaminated with the Vincent organism. H. L. Lillie has expressed himself as believing that Vincent's angina is not an entity and that the saprophytic picture which it represents may complicate streptococcus infections and a variety of ulcerative lesions in the throat.

Darkfield Diagnosis.—Mahoney and Bryant (1934) pointed out that even expert observers did not agree on the differentiation with respect to *Sp. pallida*, of certain oral (tonsillar) spirochetes. In 40 per cent of tonsils examined confusion was possible.

Constitutional Symptoms Deceptive.—The constitutional symptoms accompanying marked infections of the tonsils do not always eliminate chancre from the diagnosis, for saprophytic or secondary infection of a syphilitic primary lesion may easily give rise to incidental symptoms of malaise, local pain, arthritides, and arthralgias, loss of weight, and other symptoms of systemic reaction. Such constitutional symptoms are moreover not uncommon in the preeruptive or secondary incubation period of syphilis with an uncomplicated primary lesion. Thus, although entirely legitimate accompaniments of a chancre in the throat, the constitutional symptoms may create the impression that the lesion is due to some other type of infection and deflect attention from the true state of affairs.

Satellite Adenopathy in Lip and Mouth Chancres.—Satellite bubo in lesions about the lip and buccopharyngeal cavity usually involves the submental and anterior cervical groups of nodes as has been stated and apart from somewhat greater conspicuousness, a *strict unilateral character* and solitary tendency presents the usual features of the satellite adenopathy of the chancre elsewhere on the body. The easy accessibility of this bubo to darkfield study by node aspiration, which eliminates errors due to contaminating mouth organisms is of material assistance in the diagnosis of lesions within the throat. Systematic study of such localized adenopathies associated with throat lesions should yield a very fair return in extragenital chancres which would not otherwise be diagnosed until the appearance of secondaries, or

which would because of inadequate general examination, be overlooked entirely until in later life the patient appears with other evidence of syphilis. The confusion of massive satellite lymphadenopathy with lymphosarcoma is emphasized by several case histories in this text. Clodfelter (1936) reports a case in which a syphilitic primary bubo was diagnosed as Hodgkin s disease by clinicians and a competent pathologist with recovery under anti-syphilitic treatment.

Chancre of the Nasal Septum—This rare type usually observed in physicians, is seldom diagnosed.

Chancres of the Finger and Hand.—Of the remaining types of extragenital chancres, those involving the finger and hand deserve special mention because early diagnosis of such lesions is all but unknown owing to the low threshold of suspicion regarding them. Medical men themselves, and those associated with them in the care of the sick, are the most frequent victims.



Fig. 242.—Chancre of the index finger in physician who, following the advice of several colleagues, came t have his finger amputated for sarcoma. *The Spirochaeta pallida was bundant,* the blood Wassermann reaction positive, but no secondaries had appeared. There was febrile therapeutic shock following the first arsphenamine injection.

Fournier states that of 49 chancres of the hand hich he had seen, 30 ere in physicians, and that the infection as most often the result of manipulations involving the genitalia both in diagnosis and operative ork and in digital explorations of the mouth cavity This statement holds good today Obstetrical procedures, dental manipulations nd bare-handed tonsillectomy are defini sources of danger Wile and Holman (1941) observed chancre of the palm in physician who arrived t an obstetrical delivery in time to exert bare-handed pressure on the presenting head. Among laymen digital chancres from genital contact hile not common seem t escape diagnosis consistently and the bru l chancre of the knuckle from inoculation following blow on the mouth of syphilitic is seldom identified short of the ppearance of secondary lesions, if then

It is highly important to bear in mind certain points about the chancre of the finger While an abrasion or hangnail is a common starting point, it is not a necessary one Actual solution of continuity is not necessary The clinical appearance of the lesion exhibits the widest variability Erosion or ulceration may not occur and the lesion may present no more than the appearance of a mild paronychia At the other extreme the digital chancre of the tip of the finger may develop into a beefy-red granulating, fungous lesion which seems to suggest sarcoma (Fig 242) more often than any other clinical diagnosis

This lesion, like the felon chancre, may be intensely painful, a fact which has been responsible for many errors in diagnosis The physician s suspicions are set at rest because he has been taught that the typical chancre is painless The felon chancre as its name indicates is a painful bulbous enlargement of



Fig. 243 —"Felon chancre" in hospital attendant. The lesion healed after two incisions for supposed whitlow The patient then appeared with secondary syphilid.

the tip of the finger which seldom escapes without at least one incision (Fig 243) in the effort to evacuate pus that may or may not materialize. The finger may serve as the point of inoculation for syphilis without the development of any local reaction whatever The 4 cases which withstood Almkvist s critique

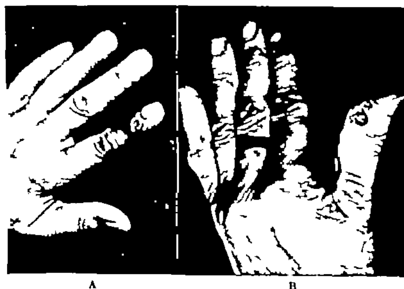


Fig. 244 —Tularemic chancres of the fingers. They are accompanied by satellite adenopathy (Courtesy of Dr C. N Kavanaugh.)

of reported instances of syphilis d emblée were all needle-prick inoculations. Operating upon untreated and especially early syphilitic patients is therefore a particularly risky procedure for needle prick inoculation is the one definitely established method in man of acquiring syphilis without even the warning

of a chancre Darkfield examination of a suspected digital chancre especially within the first two weeks of its course yields excellent returns in early diagnosis We feel no hesitation in saying that it should be an absolute rule among medical men to have darkfield examination of any lesion about the finger even though trivial, which does not heal within this period Those who make barehanded vaginal examinations and operate without gloves should be particularly alert in this matter This applies especially to gynecologists and otolaryngologists.

Fig. 245

DIFFERENTIAL CONSIDERATIONS IN "PHYSICIAN'S CHANCRE"
(The Chancre of the Finger and Hand)

1 Simple infection—more acute and inflammatory; more rapidly progressive (hours or days rather than days or weeks); visible, early lymphangitis (?) softening of the gland fever and septic symptoms. Pain is not of differential value. Darkfield negative, BWR negative unless intercurrent syphilis.
2. Inoculation tuberculosis—indolent or chronic, lymphangitis delayed, noninflammatory, cordlike gland may follow partial healing of lesion; softening or adherence of gland apple-jelly nodules in periphery of primary (Fig 230 A) Darkfield negative, BWR negative, unless intercurrent syphilis.
3. Sarcoma—including melanotic whitlow—slow development, late adenopathy pigment deposits or bone changes. Darkfield negative, BWR negative unless coincident syphilis.
4. Epithelioma—keratoses often present, rolled border ready bleeding late adenopathy delayed course.
5 Tularemia—adenopathy first and painful only later (twenty-four hours) A painful, swollen, inflamed papule, breaking down with necrotic core, punched-out ulcer with raised margin, healing with scar Darkfield negative. Lymph nodes suppurate and discharge Subcutaneous nodules suggest sporotrichosis. Chills and fever
6 Sporotrichosis—nodule, early suppuration, subcutaneous softening nodules along lymphatic chain; early suppurative lymph nodes darkfield negative, positive culture
7 Rat-bite fever—history of bite, ready healing, twelve to thirty day incubation, pain, swelling, lymphangitis, visible red streaks usually preceded by chills, fever May ulcerate.
8. Anthrax —angry inflammatory papule or papulopustule, developing dark or black necrotic center early fever, palpable, tender satellite lymph nodes, local spread.
9 Foreign body reaction—tender papule mildly inflammatory No erosion, sticking pain pressure, no adenopathy
10 Erysipeloid—history of fish, crab, or meat handling vesicopustule inflammatory healing and followed by migratory erythema as high wrist local tender adenopathy

MAKE A DARKFIELD EXAMINATION OF EVERY INDOLENT LESION OF HAND OR FINGER ASSOCIATED WITH LOCAL ADENOPATHY

The satellite bubo of the chancre of the finger or hand is usually the swollen epitrochlear node. At times however the reaction takes place in the axillary group where it may be overlooked unless a search is made for it. We have seen the node excised and incised as tuberculous

The differential possibilities are summarized in Fig 245 and include simple infection, felon, inoculation tuberculosis, sarcoma epithelioma tularemia, sporotrichosis, rat bite fever anthrax foreign body reaction erysipeloid

Chancre of the Eyelid.—Chancre of the eyelid (Fig 246) deserves mention among the types of onset of syphilitic infection among medical men Two of four such lesions which Stokes saw were in physicians and in none did the ophthalmologist consulted make or even suggest the diagnosis. In both cases the higher threshold of suspicion of a syphilologist, and an appeal to the ever

ready darkfield established the nature of the condition. Droplet infection from coughing patients and transfer of material to the eye by a careless gesture are the principal modes of inoculation.

Chancre of the Nipple.—Of chancres of the remainder of the body the nipples are conspicuous sites in women but are rarely involved in men. With



Fig. 246.—Chancre of the lower eyelid in physician. Thought to be exogenous infection. *Spirochaeta pallida* demonstrated by darkfield.

the application of the Wassermann test to wet nurses, and a better comprehension of the standards of examination appropriate in such cases the nursing chancre has become much less common. The principles laid down for detection of this type of primary lesion granted a proper degree of alertness in the physician do not differ in any particular from those applicable to other types of primary lesion.



Fig. 247.—Chancre of the neck, treated for two weeks as "furuncle." Note the ecthymatous ulcerative character of the chancre on the skin. The bubo lies immediately beneath and posterior to the lesion. The patient secondary eruption, mild macular syphilid, unrecognized, is shown in Fig. 261. It is not wise to diagnose, dress, or treat chronic lesions of the skin without completely examining the body surface. The *Spirochaeta pallida* was found in small numbers in this lesion.

Chancres on the Skin.—It should be borne in mind in general that the appearance of a chancre on the skin of the body is usually markedly different from that of the lesion on mucous and mucocutaneous surfaces (Fig. 247). The chancre of the skin is more apt to be crusted and ecthymatous in appearance does not present the definite circumscribed induration of the base found in looser and thinner tissues, and on removal of the crust is often found to be an ulcer with a raised margin rather than an erosion. The recognition of such lesions in the first few days of their course is more than can reasonably be

expected of the average physician If however the criteria of chronicity and satellite adenopathy be recalled, an alert observer will usually find his suspicions aroused by the evolution of the lesion within the first two or three weeks

Anorectal Chancre.—The anal chancre resulting usually from pederasty varies considerably in morphology A typical Hunterian primary lesion may



Fig 248.—Anthrax pustule (shaving brush infection) with satellite bubo. The ring of rapidly spreading edema with central gangrene is distinctive. Lesion five days old.

be present at the external ring or on the adjacent skin. Occasionally a hemorrhoid may be transformed into an indurated primary lesion. Diffuse brawny infiltration of all or part of the external or internal ring may occur and multiple fissured chancres may also develop Ault (1937) in a critical review states



Fig. 249 —The distinctive rolled pearly border of solitary basal cell epithelioma of the hand

that the anal chancre most commonly resembles posterior fissure and begins as a clean ulcer with a ragged edge and subsequent secondary infection.

Case Histories of Extragenital Lesions.—The following case histories illustrate more vividly than any purely descriptive presentation the unexpected onset and the ineffectiveness of incomplete precaution in preventing infection with syphilis Two of the cases illustrating the gynecological and

otolaryngological chancres, so to speak, are rendered in dialogue almost literally as they occurred

Case History.—A young man was sent for examination after four weeks of treatment had failed to heal an indurated paronychial lesion on the outer aspect of the nail bed of the right middle finger Although college student, the patient orked during spare time in garage and gave history of having bruised the finger slightly at the site of the lesion while cranking a car

Fig 450.

THE EXTRAGENITAL CHANCRE IN THE PHYSICIAN

Three Doctors, Three Students, Three Weeks

Doctor No. 1.

12/10/31 Nicked thumb with glass ampule fragment in barehanded obstetrical delivery
12/20/31 "Infection. Incised. Hot wet dressings. -Ray picture. Blood Wassermann reaction negative. Other chemistry negative.
Right axillary denopathy
3/3/32 General rash.
Diagnosis "Septic eruption.
3/25/32 Neo 0 3 Gm. given for "Vincent infection of mouth (not for syphilis).
3/26/32 On insistence of son (M. D.) Kahn test done, reported 4 plus.
3/28/32: Treatment begun.

Doctor No. 2.

2/11/32: Sore, right index finger noted.
Had done barehanded tonsillectomies and local treatment on 3 syphilitic throats.
3/10/32 Axillary adenopathy
Node excised.
3/15/32 Fever malaise, rash.
Diagnosed chickenpox.
3/24/32 BWR strongly positive.
3/25–29/32 Three injections neoarsphenamine with explosive reactions. "Given Pho-eti—like hypodermic, doctor
3/31/32 Sent for advice as to "intolerance

Doctor No. 3.

3/10/32 Did barehanded circumcision on patient with gonorrhea, later discovered to have condylomas ed ani and BWR positive.
4/2/32 Finger sore.
4/3/32 Darkfield negative. BWR negative. Five darkfields & BWR negative since.
4/15/32 Darkfield positive. Axillary adenopathy
4/16/32: Darkfield again positive, 3–4 pallida per HP field. Kolmer Kahn, Kline tests negative.
4/16/32 Treatment begun.

Comment

1. Seven doctors participated in this three weeks of tragedy as observed in my office. Three of them are former students of mine, two of whom figured on the right, one on the wrong side of the diagnosis.
2. All the three victims were caught by technical slips that sooner or later lead to trouble
   (a) Barehanded operating on throat and genitals.
   (b) Operating on patients with active syphilis not recognized.
   (c) Operating on early syphilitic patients not sterilized (one dose of "914") before operation.
3. One victim had repeatedly exposed his wife.
4. Only one (No. 3) followed the proper course after sore appeared, and began treatment while seronegative. He was urologist.
5. The other two illustrate most of the blunders that can be made in diagnosis and treatment.
6. The "index of suspicion makes the diagnosis of syphilis. "How shall the blind lead the blind?"

"PHYSICIAN HEAL THYSELF"

The lesion was therefore interpreted as banal infection. When seen by the syphilologist the satellite bubo and positive darkfield on aspiration established the lesion as chancre. He was then more closely questioned as to his activities, and admitted exposure the evening of the accident in cranking the car. He disavowed titillation, pparently truthfully but recalled having used the second and third fingers of the right hand to separat the labia. Following the exposure he took vigorous genital prophylaxis, but forgot to include the finger upon which his chancre subsequently developed. W have seen chancres develop simultaneously on both penis and finger under similar circumstances without prophylaxis.

Case History—A young man presented himself in the clinic complaining of pain on defecation. A proctoscopic examination, while only partly successful because of the excruciating pain, revealed some redness of the mucocutaneous junction about the external ring but no ulceration. There was palpable doughy infiltration, exquisitely tender. A Wassermann test was strongly positive and the patient was thereupon sent to the dermatologist, who found him to be in the florid eruptive secondary stage of syphilis without any visible sign of primary lesion. The personality of the patient was not such that an anal chancre from pederasty seemed possible. The patient was urged to remember as closely as possible the circumstances of his recent sexual experiences. Following successive exposures at about the proper interval before the appearance of the lesion, he had gone at once to a medical friend who had supervised a thorough genital prophylaxis. While the details could not be corroborated by confrontation, it appeared highly probable that he had developed an anal chancre from mediate transference of the virus to the anal ring by the partner's finger, his prophylaxis having protected him from a genital lesion. We have seen similar mediate transference in a case of chancre of the abdomen in which the penis itself escaped apparently as a result of prophylaxis, although acting as the transmitting agent before prophylaxis was applied.

Case History—A gynecological surgeon stopped me on a street corner about some trivial matter. As we conversed, he rubbed his right index finger.

"What is that?" I asked.

"A little infection, I guess," he replied.

The finger presented a very slightly reddened, slightly raised swelling along the nail margin—no erosion, no ulceration—scarcely a lesion of any sort, in fact.

"Come on out with me and I'll darkfield it."

"Oh shucks, it's nothing. Getting better too."

"Better have it darkfielded anyhow. Little things like that in gynecological men are apt to be serious."

"Never mind, there's nothing to it."

This was the last I heard of it for the time. A year and a half later I was told by the physician who had treated him that he had developed secondaries. He wanted me to know of it because I had made his diagnosis on a street corner. At no time had the primary lesion on the finger deserved the name of chancre.

Case History—Two surgeons were arguing with an otolaryngologist in the opposite sleeping car section.

"Let me drill a hole in that nail. I'll bet you there's pus under it."

The otolaryngologist had a slightly raised paronychial lesion of a week's duration about the nail of the right index finger with some blueness of the nail bed. He consented reluctantly and, after sterilizing the blade of a pocket knife with a match flame, one of the surgeons drilled a hole through the nail. To the disappointment of all, no pus appeared. In the meanwhile I had inspected the lesion from the arm of the seat, and at a distance of 4 feet had felt the "hunch" of intuitive syphilological diagnosis.

"I'll give that 90 per cent for a chancre," I ventured.

I received the visual signs of incredulity from all present.

"You do nose and throat, don't you, Doctor?" I proceeded boldly.

"Yes."

"And strip the capsule with your finger?"

"Yes, I got that technic at the X—— Hospital."

"Whom did you operate on a month ago, can you recall?" I asked.

"By Jove that's right—we took a Wassermann later when her throat didn't heal and found it was positive."

"There you are," I finished. "As soon as you get to M—— I want you to go to Y—— and get him to do a darkfield on that finger instanter and, if it is positive, begin treatment."

"Nothing to it," was the nose and throat man's verdict.

I appealed to one of the surgeons, who promised to back my instructions with force if necessary. Four days later I was passing through a hotel corridor when the surgeon who had drilled the nail came up to me and spoke sharply in my ear the words "Teeming with spirochetes."

CHANCROID, LYMPHOGRANULOMA VENEREUM, GRANULOMA INGUINALE

Because of the frequency with which the diagnosis of syphilis is entangled with certain other venereal diseases, a brief working description, by no means complete, is offered to round out the presentation of the primary syphilitic lesions.

Chancroid.—In syphilologic perspective the diagnosis of chancroid has a negative rather

than positive significance. So long as morphologic criteria held the center of the stage chancroid provided a pitfall for the unsuspicious and inexperienced diagnostic mind or for those who instinctively tend to avoid a diagnosis of syphilis as long as possible. This was quite apparent in the experience of the American Expeditionary Force during World War I in which the tendency of men without special venereologic experience to diagnose chancroid in genital lesions, which ultimately proved to be double infections, was a serious breech in the diagnostic ramparts. Chancroid is a local ulcerative process (in rare instances, Milian has insisted that there may be systemic complications) whose syphilologic importance consists in the fact that it may simultaneously be the site of development of a primary lesion of syphilis.

Admirable monographic presentations of chancroid as such have been published by Maurice Sullivan (1940) and many valuable investigations by the Cleveland City Hospital group headed by Cole. Major Greenwald's (1943) summary well presents the army problems and methods.

Chancroid, ulcus molle or soft chancre, is an acute localized autoinoculable venereal disease caused by the streptobacillus of Ducrey (*Hemophilus ducreyi*). The local genital lesion is a non-indurated tender ulcer with an incubation period averaging three or four days, but as long as twelve or even twenty-two or more days (Greenwald). The ulcers are irregular, present a granular dirty grayish base covered with a small amount of grayish purulent exudate and with slight undermining at the edges. Free bleeding follows manipulation. The ulcers are more frequently multiple than single and tend, because of their autoinoculability, to become more numerous the longer the course of the disease. The commonest location is at the edge of the phimotic prepuce or in circumcised males, on the frenum and in the coronal sulcus. Fifty-four per cent of Greenwald's patients presented involvement of the inguinal lymph nodes on reporting. Pain is common in the more advanced stages, and is occasionally attended with fever and anorexia.

Venereologically it is interesting that chancroid is much more frequent in men than women, although it is believed that women may be asymptomatic carriers of the *Hemophilus ducreyi*, and it has even been suggested by Brams (1944) that this organism may be found in some males as a saprophyte in the smegma of the coronal sulcus. The incidence in Army practice, as between Negroes and whites was, in Greenwald's experience in a ratio of 120 : 1—a disproportion which does not appear in the incidence of gonorrhea or syphilis. Chancroid is notably more resistant to prophylactic measures than the other venereal infections (Greenwald) and according to this observer soap and water particularly advocated for prophylaxis, is not effective.

The most annoying complication of chancroid, the suppurating bubo, is usually unilateral with matting or fusion of the enlarged glands after a lapse of time, the development of fluctuation, and unilateral suppuration following. Spontaneous healing or extensive ulceration may follow such spontaneous rupture. Ravechkolb, particularly studying the factors leading to the development of bubo, formulated the following axioms with regard to it (1930).

"The smaller and more inaccessible the ulcers are to therapy the more likely the occurrence of buboes.

"Conversely the larger and more accessible to therapy the lesions are, the less the incidence of buboes.

Caustics or actual cautery predispose to the development of adenitis.

"Lesions so situated as to produce phimosis and poor external drainage are more apt to initiate adenitis than are lesions on the cutaneous surface of the prepuce or the shaft of the penis.

Induration is not ordinarily a characteristic of the chancroid in the male or female, except as the result of cautery or irritant treatment, and its spontaneous appearance should always arouse suspicion of a double infection with syphilis.

The diagnosis of chancroid as well as its treatment has been materially advanced in recent years. The smear, with identification of the organism by a Gram stain, Wright stain, or methyl green pyronine is now so satisfactory in competent hands that Kornblith, Jacoby and Chargin (1941) rated its efficiency at 89 per cent, and Greenwald at 65 per cent. The "school-of-fish-like" arrangement of the organisms among the leukocytes of the smear is rated as specially characteristic. The complement fixation tests have been rated as unreliable, but the Ito-Reenstierna intradermal tests have a high degree of specificity and, like the tuberculin test, have great negative as well as positive significance, because permanent skin sensitization for the antigen apparently results from an attack of chancroid at any time in life. The time required for the test to become positive, which is important in early diagnosis, is rated by Speiser (1944) as low as six to ten days, and by Becker and Obermayer (1940) at a minimum of five weeks. Competently examined smears and intradermal tests (in this connection the Cole-Levin pus antigen (1935) also deserves mention) should make possible an expeditious positive diagnosis of chancroid in the majority of cases.

The diagnostic problem of chancroid with respect to syphilis, is, however, not met unfortunately by the positive diagnosis of chancroid. Greenwald has most recently insisted that four successive examinations by darkfield have, in his experience largely eliminated the necessity for

the serologic follow-up of blood-tests through the ensuing three to four months. In military practice such incomplete procedure may be enforced by exigency but in civilian practice, the necessity for proving that a chancroid has not been complicated by the onset of syphilitic infection requires invariably and unconditionally the repetition of serologic tests for syphilis on the blood at intervals of a week for one month following the recognition of the chancroidal lesion and once a month thereafter for an ensuing three months. This, the so-called serologic follow-up, is as integral to the air-tight exclusion of syphilis from the diagnosis of chancroid as it is to the exclusion of syphilis as a complication of gonorrhea.

Treatment of Chancroid.—This has been revolutionized by the advent of the sulfonamides. Formerly advanced, rapidly progressive and resistant lesions required every ingenuity of local treatment with soaks and compresses, drainage without rash surgical intervention, and the use of various preparations locally. Out of reach of the sulfonamides, potassium permanganate provides the one probably safest single controlling measure—the hot potassium permanganate soak in a concentration of 1:6,000 to 1:10,000 aqueous solution. With the sulfonamides the answer to the chancroid is sulfathiazole, 4 grams in divided doses for each of seven successive days (10 days, Kornblith).

Other methods of local treatment include soaks with 1:8,000 mercury bichloride solution, dilute copper sulphate solution with fulguration (Robbins and Seabury, Jacob); and, once the lesion is comparatively clean, dusting with iodoform or thymol iodide. An alternative in the case of sulfonamide sensitivity is tartar emetic (Gutmann, Jones), a one per cent solution given intravenously starting with 3 cc. and increasing 1 cc. per injection up to 10 cc. given twice a week (see ulcus molle serpiginosum).

Ulcus Molle Serpiginosum.—This condition, often regarded as chronic chancroid, and often spoken of also as phagedenic chancroid, is not to be confused with the fulminating Vincent infection of the genitalia known as gangrenous balanitis (p. 488). None the less, it is one of the most alarmingly destructive of the entire group of genital lesions and, once its determined march through the skin and subcutaneous tissues is begun, it can be arrested only by almost heroic effort. The essential unit of the ulcus molle serpiginosum picture is the kidney-shaped ulcer with undermined, overhanging, and indurated border, a dark hemorrhagic base and "hilus" of scarred and healing tissue on the convexity of the kidney-shaped lesion. A combination of such units produces the serpiginous border characteristic of the condition and the resemblance at times to late syphilids may be startling and leads to errors in diagnosis. It is not at all an uncommon thing for a single lesion of this type to begin near the base of the penis and to sweep penis and testicles before it in a gradual though sometimes fairly rapid advance, literally "cleaning out" the inguinal and perineal region and extend backward upon the buttocks in a course ranging from six months to three or more years. Patients of this type undoubtedly present a special predisposition of some sort, an increased susceptibility particularly of the subcutaneous fat and connective tissue which makes them an easy prey. In dealing with such a case the physician may confront one of the most difficult of therapeutic problems. The simpler methods already described having failed, even though syphilis is not responsible the patient may be given neoarsphenamine intravenously and potassium antimony tartrate in alternation, and the actual cautery vigorously used in the effort to stop the progress of the advancing lesion. Under local or gas anesthesia the ulcers may be trimmed flat, every trace of the rolled undermined border being done away with and thoroughly cauterized. Pyrogallic acid, beginning with 10 per cent strength and increased to full-strength applications, has been commended where the cautery has failed. In two refractory examples, radium, used to the point of pronounced reaction, gave highly satisfactory results after everything else had failed. Skin grafts may be used to cover denuded areas and hasten epithelialization and sulphhydryl wet dressings and ointments containing oxyquinoline derivatives, among the newer possibilities, might deserve trial.

Lymphogranuloma venereum.—The disease entity designated by this name, official for the American Medical Association, has emerged from the miscellaneous collection of hypertrophic and ulcerative infective processes involving the genitalia and the lower gastrointestinal tract as well as other structures, described through the last quarter-century by a wide variety of terms. Lymphogranuloma venereum is a systemic virus disease with primary localization in the lymphatic system with spread to adjacent structures and now quite well-recognized systemic manifestations. Its importance in the diagnosis of syphilis as well as in venereology in general justifies a rather detailed description of the clinical manifestations.

The virus itself was probably first seen by Gay-Prieto (Findlay) in 1933. It belongs to the lymphogranuloma venereum-psittacosis group of virus diseases which includes trachoma, inclusion conjunctivitis, psittacosis, human atypical pneumonia, acute meningopneumonitis, and mouse pneumonitis (Rake and Jones, 1942). Formerly believed to be a disease of tropical countries, it is now apparent that its distribution is world-wide and demonstration of its prevalence

the persistence of the infection, once established in the individual, the long duration and recurrence of infectiousness, all make it a disease of grave public health significance. Its association with sexual promiscuity while definite, is by no means exclusive. The Negro, as in the case of syphilis, is overwhelmingly more affected than the white race. The anorectal syphiloma and esthiomene, the elephantiasic ulcerative form of lymphogranuloma venereum involving the external genitalia, were for years rated as syphilitic or tuberculous in origin by the most unimpeachable authority. Fournier's description of tertiary lesions of the anus and rectum, "syphilome anorectal" is probably composed almost entirely of the physical characteristics of lymphogranuloma venereum.

Six groups of clinical manifestations afford a convenient classification (according to Grace) on which to base the clinical description of lymphogranuloma venereum. These include:

1. The genital variety of the disease.
   (a) Erosive penile lesions.
   (b) Erosive vulvar and vaginal lesions including esthiomene.
   (c) Elephantiasis of the external genitalia.
   (d) Abacterial urethritis.
2. Inguinal variety of the disease.
   (a) Inguinal adenitis, suppurative and nonsuppurative.
3. Pelvic variety of the disease.
   (a) Inflammatory disease of pelvic tissues.
4. Anorectal variety of the disease.
   (a) Perianal edema, ulceration and hypertrophy.
   (b) Fistula in ano.
   (c) Perianal abscess.
   (d) Anal and rectal stricture.
5. Colonic variety of the disease.
   (a) Ulcerative colitis?
6. Extragenital variety of the disease.
   (a) Manifestations dependent on the site of infection and its associated lymphatic drainage.

Manifestations in other systems are:
   (a) Eye (changes of vessels of the fundus, peripapillary edema, conjunctivitis).
   (b) Bone and joint.
   (c) Nervous system (meningo-encephalitis, meningeal).
   (d) Skin (lymphogranulomatid, photosensitivity).
   (e) Other scattered localizations (upper respiratory, gastro-intestinal, genito-urinary, muscular).

The clinical course of lymphogranuloma venereum of genital origin may be briefly described as follows. The primary sore or lesion usually appears from two to five days after the infective coitus. In the male it is most commonly observed on the coronal sulcus but may appear on the glans, the prepuce or in the urethra. There may also be a balanitis. In the female the inoculatory lesions may occur on any part of the external genitalia, the usual site being the posterior vaginal wall, posterior lip of the cervix, or in the neighborhood of the fourchette. The lesion is a small herpetiform vesicle or ulcer, circular or lenticular, sometimes multiple, with clean-cut edges surrounded by a reddened zone, but with no induration or infiltration. The base of the ulcer is whitish gray and forms a small rounded hollow of pin-head size. The lesion is asymptomatic, heals spontaneously and is often missed both by the patient and the physician. The incubation period is one week or less in 70 per cent of cases, but may be as long as five weeks. The lymphotropism of the virus leads to the development of a bubo in the drainage area of the primary lesion. The incubation period for this manifestation from the time of infection ranges from four days to more than 100, and is most frequently ten to twenty-nine days. The early impression that lymphogranuloma venereum was exclusively a disease of males, as well as the failure to identify the vulvar and anorectal granulomas with lymphogranuloma venereum was a consequence of the lymphatic distribution of the virus. When the primary lesion occurs in the inguinal lymphatic drainage area, whether in male or female, inguinal buboes and esthiomene are the prevailing manifestations. When inoculation occurs in the vagina or upon the cervix, direct extension of the infection through the rectovaginal septum leads to the syndrome of anorectal lymphogranuloma. The bubo localization is prevailingly inguinal and iliac, more frequently the latter, and more frequently unilateral than bilateral. Occasional inguinal, femoral, and inguinofemoral and iliac involvements occur. From the secondary adenopathy first recognized by the patient through a sensation of stiffness and aching followed by swelling, the process may come to an end, or after retrogression, may light up again. The person may then remain a carrier of the virus without active symptoms for

many years The infection usually extends however until all the nodes of the group are involved, with considerable periadenitis, the nodes becoming fixed and adherent to the skin. Inflammatory changes continue, with softening and the formation of abscesses and fistulae, from which characteristically thick, viscid, tenacious opalescent, yellowish-white pus exudes, and from which no organisms can be demonstrated by the usual cultural methods. In a period usually extending from two months to two years, the glandular swelling subsides, drainage is complete, and healing takes place. If the destruction of nodes and surrounding tissue is widespread, secondary elephantiasis of the leg and pudenda may follow or there may be a complicating phlebitis. Extensive and central suppuration of the lumbar nodes, extensive destruction of the psoas muscle, and extension of the infection to articular surfaces, to the kidneys and adrenals of the involved side have all been observed.

The constitutional manifestations include slight fever slight leukocytosis with mononucleosis, increased sedimentation rate and hyperglobulinemia, especially in the later stages. Pulmonary involvement, ocular lesions with regional adenopathy tonsillar ulcers, ulcerative angina,



Fig 2-1 —The primary lesion of lymphogranuloma venereum. (Courtesy of Dr Arthur W Grace, New York)

arthritis at points distant from the site of initial involvement, occasionally simulating rheumatic fever or purulent arthritis, have been recognized. The dermatological manifestations include erythema multiforme erythema nodosum, scarlatiniform eruptions, papular lesions, ulcers and giant keloid formation. Particular interest attaches to the characteristic lymphogranulomatids reported by Saenz (1935) and by Goldberg and Fondé (1936) which are indicative, theoretically at least, of vascular dissemination and allergic characteristics in the disease.

The late lesions of lymphogranuloma venereum include the anorectal syndrome genital elephantiasis with ulceration (esthiomene) and some of the remote system types of involvement just mentioned Of these the anorectal syndrome consisting of inflammatory strictures of the rectum, represents in all probability the most serious form, and occurs predominantly in women Grace (1945) divides rectal involvement into the following clinical types (1) stricture with proctitis (2) stricture without proctitis, and (3) proctitis without stricture Most cases of proctitis without stricture had no history of previous anorectal disease The rest had had perirectal abscess or fistula in no t average interval of 1 7 years About one-third of these cases develop stricture

Unless stricture develops within three years after the onset of anorectal inflammation, chronic proctitis without stricture will result. Men are the predominant victims of this type, and Grace is inclined t believe that the explanation lies in homosexuality In proctitis with stricture, fibrous band, usually single, may extend over several inches of the wall, and occurs most frequently within reach of the examining finger The condition is chronic accompanied by bloody purulent anal discharge, and in the absence of fissure with little pain. An eight millimeter diameter will permit evacuation with the aid of cathartics. The average period before colostomy became necessary (60 per cent of cases) was 7.8 years. Fistula in ano, rectovaginal fistula and perirectal abscess were sequelae in one-sixth of the cases.

Stricture without proctitis develops from outside the bowel wall and is most common in women (61.3 per cent) Stricture without proctitis presents the ppearance of scar tissue diaphragm across the lower bowel with small central aperture. Involvement of the gastro-intestinal tract above the rectum has been subjected to considerable study and controversy for which reference should be had to the papers of Rendich and Poppel (1939) and Paulson (1936, 1941)

Genital Elephantiasis with Ulceration (Esthiomene).—In the earliest phases, small noncharacteristic ulcers of the vulva, anus or rectum may occur which persist, enlarge and disappear only to reappear Elephantiasis consists of moderat to marked swelling of the labia majora and sometimes of the labia minora, urethral and anal folds which form round hemorrhoid-like or lobulated cockscomb-like masses. The involvement of the labia is usually bilateral, one side being more affected than the other and occasionally the clitoris participates in the elephantiasis to such an extent that it may be hypertrophied to ten or fifteen times its normal size and may undergo secondary ulceration. In some cases only abortive forms are seen for a long time such as swelling of the vulva without ulceration, swelling of the anal folds; chronic recurrent abscesses of the vulva, buttocks and so forth. In the male, similar elephantiasis of the penis and scrotum with or without ulceration may occur but is much less common as sequel than in the female. It may occur after surgical extirpation of the inguinal nodes, but also independently

Secondary infections such as erysipelas, severe pyogenic invasion and occasionally carcinoma may occur on the elephantiasic tissue Combinations of the anorectal and genital syndromes are not infrequent. The special student of the rectal pathology and clinical manifestations should read the papers by Cole (1933), by Van der Veer Cornan, and Ullery (1933), by Mathewson (1938), by Bloom (1934 1936) by Bensaude and Lambling (1936) and Stannus (1934)

The Skin Diagnostic Tests.—The importance of lymphogranuloma venereum in venereologic diagnosis and its world-wide prevalence and probable frequency make the performance of diagnostic test for the disease reasonable requirement in every venereologic work-up. The basis for such test was supplied by Frei in 1925 with the discovery that the pus of the inguinal bubo contained antigenic properties which enable it t be utilized in highly specific intradermal test. The technical details of the preparation of the Frei antigen will not be reviewed here, since it seems in process of displacement by the yolksac antigen developed in Rake laboratory and marketed as Lygranum (ST) (McKee, Rake and Shaffer (1940)) Those desiring to review it will find usable description in the report by Beerman, Ingraham and Stokes (Am. J Med. Sci. 197 892, 1939) In 1934 Grace and Suskind described mouse-brain antigen which is effective if controlled with normal mouse-brain emulsion now invariably used to detect nonspecific effect. Rake points out however that the concentration of virus is low leading to doubtful or negative results in patients who undoubtedly have had the specific infection. *The technic of the Lygranum test,* according to the manufacturer instructions and Axelrod' publication (1942), is as follows. 0.1 cc. of the virus antigen and an equal amount of normal chick embryo yolk control is injected t separate sites intradermally into the skin of the forearm, previously prepared with alcohol. Readings are made t forty-eight hours and seventy-two hours, and in many cases were repeated by Axelrod at the end of eek. In interpreting the results of the tests, only the inflammatory indurations were taken into consideration. In the case of erythema, regardless of its extent, whether alone or as zone surrounding papule, it is not considered significant. By positive tests are meant those in which the papule measures at least 7 7 mm. By doubtfully positive reaction is meant one in which the papule is less than 7 7 mm. but more than 5 5 mm. In negative reaction the papule measures less than 5 5 mm.

A complement fixation test employing the yolksac antigen has been used by Shaffer Rake and Grace (1942) and is still in the process of evaluation. One of the objections to it is the tendency to cross positive reactions with other diseases of the lymphogranuloma venereum-psittacosis group but since these are relatively rarely involved in the diagnosis of syphilis, the complement fixation test ith Lygranum CF when evaluated. may be serviceable in detecting the norectal syndrome and so forth.

There are number of indications that cross reactions occur between syphilis and lymphogranuloma venereum in the field of skin and complement fixation tests, and that biologically

false positive serologic test for syphilis may occur in cases of lymphogranuloma venereum accompanied by hyperproteinemia (Cardon, Atlas, Aron, Brunner, Teitelman and Busata (1942).) The precise proportion of biologic false positive serologic reactions for syphilis in lymphogranuloma venereum is yet to be determined.

Treatment.—The use of the sulfonamides and antimony has greatly improved, if not as yet completely solved, the treatment situation in this disease. Grace (1943) employing sulfathiazole in the early stages of lymphogranuloma venereum advises 1.5 grams administered orally three times daily for two weeks, and then one gram three times daily for the next two weeks. A rest period is then allowed, during the succeeding three weeks, after which treatment is resumed, beginning with 1.5 grams three times daily as above. In inguinal cases a second course is not usually considered necessary since this is the most benign group of manifestations of the disease. In the anorectal type of the infection the sulfonamides are also efficient, particularly sulfaguanidine, in the earlier stages of involvement. The later the manifestations, of course, the less responsive to drug therapy. Antimony, effective in apparently nonspecific ways in a number of resistant genital infections and ulcerations, is also used effectively in lymphogranuloma venereum, as reported for tartar emetic and Anthiomaline (lithium antimoniothiomalate (1942) (Shaffer, Fondé and Goldberg (1939)).) Law, from a large British experience, and Shaffer (1943) in further studies, have confirmed the value of antimony. Anthiomaline is administered two or three times a week, preferably the latter—the initial dose being 0.06 gram, and the amount increased in increments of 0.03 gram until the typical rheumatoid pains appear. The dose is then reduced until the pains are just barely perceptible several hours following the injection. The tolerated dosage is usually in the neighborhood of 0.12 to 0.24 gram; the usual course consists of totals of from 2 to 4 grams—12 to 20 injections—at which point the patient is allowed from two to four weeks rest before commencing the second or final course of treatment.

The biologic therapy of lymphogranuloma venereum with Frei antigen has also been favorably reported. Prehn (1937) gives a series of at least 8 injections—one every other day intradermally—close to the site of the lymphadenitis. The intravenous use of the antigen has also been advocated, deGregorio (1937) employing 12 to 14 injections. In all estimations of therapeutic effect, the tendency of the disease to spontaneous recovery must be borne in mind.

Granuloma Venereum.—Granuloma venereum, usually called granuloma inguinale, is a chronic inflammatory process involving the upper layers of the corium, and due to a Donovan body whose recognition intracellularly in smears from tissue is diagnostic. The organism has recently been cultivated in the yolk sac of the chick embryo by Anderson (1943). Some question has been raised as to whether this disease should be regarded as venereal, though Greenblatt and his associates (1939) believe that the point of entry is most commonly about the genitalia, possibly with lymphatic distribution to the skin of the inguinal region. It is distinctly not primarily a disease of the lymphatic system as is lymphogranuloma venereum. The clinical manifestations range often successively through (1) a nodular form, which develops as a plaque 1 to 4 cm. in diameter, reddish in color and soft in consistency. Greenblatt has suggested that this be designated "pseudo bubo" since it is a subcutaneous infiltration and not a lymph node lesion. (2) The ulcerovegetative form, most common clinically, develops by excoriation and maceration with the formation of a rather spongy easily bleeding surface covered with granulating tissue. This spreads peripherally by continuity and new lesions may appear as the result of autoinoculation. In the earlier stages the granulating tissue is clean and pinkish red, the discharge serosanguineous and the surface relatively smooth, whereas in older lesions or in grossly neglected cases the surface becomes more uneven, the discharge seropurulent and foul-smelling, and the granulation tissue changes to a grayish dirty hue. The border is sharply demarcated, indurated and raised above the level of the skin, and occasionally shows a pearling suggestive of epithelioma. The process spreads along the inguinal creases and progresses for weeks and months, finally tending towards healing with trophic depigmented scars in which there is permanent loss of hair. Secondary infections are common in this stage, particularly with spirochetes, aerobic or anaerobic organisms, which tend to deepen the ulceration and necrosis of the soft tissue. So deep may such involvement be that rectovaginal fistulae and perianal phlegmon may complicate the case, ushered in with fever and general malaise. Pregnancy accelerates the pathological process, and one case of malignancy superimposed on granuloma venereum of the cervix has been reported.

The third clinical type is a hypertrophic lesion in which large vegetating masses, sometimes several centimeters high, spring from the lesion. Occasionally an elephantiasic form is observed in which esthiomene-like pictures develop, confusable with lymphogranuloma venereum. In granuloma venereum the swelling is associated with extensive scar formation in and around the involved tissue parts, whereas in lymphogranuloma venereum the skin is thick and edematous but otherwise normal. A fourth type, the cicatricial, is the result of a peculiar reaction on the part of the host to the infectious agent, leading to the formation of keloid-like lesions. The keloid

hypertrophy is not a healing or healed stage of the disease but is progressive and the Donovan body can be obtained by aspiration and seen on histologic examination of the tissue in small nests of inflammatory cells. In older cases of this type, elephantiasic changes in the labia of women are especially likely to occur.

Diagnosis is based on the identification of the Donovan body in smears, especially from the deeper tissue obtained on biopsy. Giemsa, Wright, and silver impregnation stains disclose the organism as a cellular inclusion of "safety pin" shape with densely staining nuclear or polar body at each extremity. Complement fixation tests studied by Goldzieher and Peck in 1926, have been discarded.

Treatment.—All single methods of treatment leave a certain residue of uncured cases, but skillful combination of them may result in cure. Neoarsphenamine in equal parts glycerin and cod liver oil is strongly recommended as a clean-up agent. The most effective drug is antimony whose use as potassium antimony tartrate (tartar emetic) has been standard since 1913 (Aragao and Vianna). It is given intravenously as a 1 per cent aqueous solution, the initial dose 1 to 2 cc., increasing 1 cc. every other day until the maximum of 10 to 15 cc. is reached. Two to three months of this treatment may be necessary before therapeutic response begins. While 20 to 30 injections is the usual course, 50 to 60 may be given without increase in toxic effect. The characteristic reaction consists of nausea, vomiting, diarrhea, and a rather characteristic arthralgia and myalgic pain through the shoulders. Nitritoid reactions are occasionally observed. Fuadin is also highly effective and somewhat less toxic, a 7 per cent aqueous solution being used with the initial dose 1.5 cc., increased every one to two days, up to 5 cc. intramuscularly. The report of Shaffer, Ford and Goldberg (1938) on anthiomaline (lithium antimonythiomalate) indicates that it should also be effective. The chief difficulty in the practical handling of the case is to persuade the patient to persist in treatment for a long time after lesions have healed lest relapse occur. In occasional cases, radiotherapy may assist in clinching a result obtained by other treatments. Robinson and Robinson (1914) proposed surgery for many cases previously considered hopeless. Fulguration of the edges of advancing lesions and electrocautery excision may cure patients previously considered hopeless.

Tuberculosis of the Penis.—This comparatively rare condition is usually the sequel of tuberculous ulceration of the bladder and tuberculous infection higher in the urogenital tract. The lesion is sometimes granulomatous and papillomatous, or fungating, sometimes raggedly ulcerative, involving the meatus and the lower half of the glans, and producing cicatricial contraction. Metastatic extension to lymph nodes we have not observed, though it is described, the lesion being much more suggestive of carcinoma than of any of the genital infections. Primary inoculation tuberculosis in infants following ritual circumcision has been described.

Carcinoma.—Carcinoma about the genitalia is not infrequently confused with the primary lesion of syphilis and *vice versa*. The annular carcinomatous infiltration of the meatus in women is, in fact, so similar to the annular chancre of the meatus that carcinoma is the usual initial diagnosis in such cases. The fungous hypertrophic chancre of the cervix uteri may also be mistaken for carcinoma. Carcinoma of the penis seems to bear a close relationship to phimosis, for it is extremely rare in the circumcised. It is not necessarily a disease of middle or old age. Shivers, 2 of whose 5 patients with this disease were in the third decade of life, points out that the growth exists in two forms, the papillary or cauliflower type and the indurated ulcer variety. The glans and the under-surface of the prepuce are the most frequent sites of involvement. Primary metastasis occurs to the superficial inguinal lymph nodes, followed by involvement of the deep chain and finally the iliac nodes, such involvement occurring much later of course than in the primary lesion of syphilis and being smaller and shottier. Barringer and Bean conclude that involvement of the inguinal nodes occurs relatively late and develops in less than 40 per cent of cases. The treatment is surgical destruction of the growth, local in type if the lesion is early but when the tunic of the glans is penetrated, amputation becomes necessary with extirpation of the inguinal nodes. Irradiation to the lymph gland areas suspected of involvement may be employed but the lymph node enlargement is often inflammatory rather than metastatic.

Laboratory Diagnosis of the Chancre—Darkfield Efficiency.—The efficiency of the diagnostic methods dependent on detection of the organism especially by the darkfield was tested in World War I with conclusive results.

In 1911 in the United States Army the ratio of cases recognized in the primary stage to those allowed to proceed to florid secondaries before diagnosis was made was as 1 to 7. Systematic insistence on modern diagnostic methods including the use of the Wassermann reaction reduced the ratio by 1915 to 1 to 4.5. Yet this is far from ideal and very much short of the possibilities of modern methods. Dudding and Fildes and Dudding of the British Navy in 1917 criticized the efficiency of the Royal Navy Medical Service for a ratio of 1 to 4, and pointed out that in a series of untreated venereal lesions, 65 per cent could be shown to be syphilitic at once by the darkfield alone, and that only 14 per cent of those not thus shown to be syphilitic were ultimately proved to be so by the results of subsequent Wassermann follow-up tests. This percentage sets a ratio better than 1 to 1. Figures representing the efficiency of darkfield diagnosis in the American Expeditionary Forces were reported by Moore, from the Paris district. Of 693 genital lesions, whose diagnosis represented a combination of clinical criteria and at least one darkfield examination, 54.5 per cent were diagnosed chancroid, and 45.5 per cent chancre. Of 135 cases followed for at least eight weeks after the tentative diagnosis of chancroid, and subjected to repeated Wassermann tests, 14.9 per cent subsequently became positive, showing that the original lesion was chancre and not chancroid. These percentages while lower for syphilis than those of Fildes and Dudding will be seen to coincide with them for the margin of error of the modern differential diagnosis of chancre and chancroid by the darkfield. In a table quoted below Moore compares

Fig 252

DIAGNOSIS OF CHANCRE AND CHANCROID IN THE A. E. F (After Moore)

	Total venereal ulcers.	Chancroid.	Per cent. chancroid.	Syphilis.	Per cent. syphilis.
French Army in 1916	18,900	5670	30.0	13,230	70.0
British Army in England up to April, 1917	27,000	6000	22.2	21,000	77.7
Paris clinic	693	379	54.5	314	45.5
American Expeditionary Force	3,480	2628	75.5	852	24.5

his findings with other large groups of statistics collected during the war (Fig. 252). The striking discrepancy between the high proportion of diagnoses of "chancroid" in the A. E. F. (75.5 per cent) and the small proportion of chancroids in the British and French Armies (22 to 30 per cent) Moore explains in part by the fact that the British and French diagnoses were those of experts at concentration hospitals, and hence showed a high proportion of syphilis, while the low proportion of syphilis and the high percentage of "chancroids" in the American forces represent the diagnoses of field medical officers whose acquaintance with modern methods was slight.

While it is only fair to state that part of the difference, as Moore points out, is due to a difference in the prophylactic methods employed by the various armies, the commentary on the comparative ineffectiveness of average medical diagnosis of the chancre as compared with the effectiveness of modern methods is none the less apparent.

Expectancy of Syphilis in Genital Lesions.—It is probably fair to consider that the expectancy of syphilis underlying genital lesions of all types ranges between 60 and 85 per cent with the application of all modern methods to its diagnosis. Wenger and Proske (1930) found in an examination of 1235 patients with genital lesions, that 80 per cent were of syphilitic origin and that of the 14 per cent who did not cooperate in follow-up 12 patients subsequently returned with syphilis. The overwhelming proportion of genital syphilis can be recognized by darkfield examination of the primary sore before the appearance of secondaries, before the appearance of a positive blood Wassermann or precipitation reaction in many instances and before the patient has served

as transmitter of the disease to many of his various genital and extragenital contacts

Influence of Age of Lesion.—The influence of the age of the lesion on the percentage of diagnoses made by darkfield is shown in Fig 253 from a survey made by McFarland and Stokes covering 251 cases of early syphilis, 210 of whom had either a chancre or secondary eruption, or both It will be apparent that the darkfield reaches its highest efficiency in the first two weeks of the primary lesion

Taking treated and untreated chancres alike we were able to identify 82 per cent of primary sores as syphilitic by darkfield up to the fifth week.

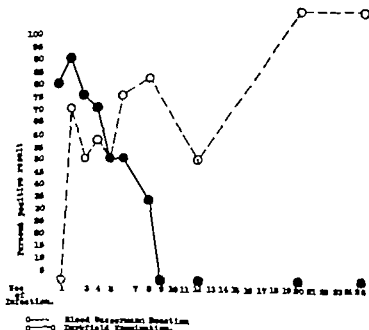


Fig 253.—Chart illustrating the proportion of positive results obtained with the darkfield examination of the chancre and the blood Wassermann reaction in the early weeks of syphilis (Stokes and McFarland)

Thereafter the percentage declines rapidly and leaves us with an average of 66 per cent positive darkfields obtained in the primary stage If the campaign for public education ultimately brings the patient to a competent examiner untreated within two weeks of the appearance of his lesion, a darkfield efficiency of over 90 per cent should not be too much to expect.

Recent Important Facts Concerning Darkfield Examination.—The Cooperative Clinical Group, which has assembled the largest material on early syphilis thus far in existence, has brought forward a number of interesting considerations regarding the darkfield and the early diagnosis of syphilis. In their material of 168 seronegative primary cases the diagnosis was made by darkfield in 91 4 per cent and on clinical appearances, presumably in 8.6 per cent. Positive darkfields were obtained on seropositive primary syphilis in 72.6 per cent, and it was possible, utilizing one lesion or another for darkfield examination to maintain and even improve this proportion of positive darkfield results throughout secondary manifestations in the first year and delayed secondary

manifestations later than the second year This means, of course, that darkfield diagnosis is susceptible of much more extended application as compared with serological tests than has been thought possible in the past The experience of our own clinic confirms this, for it is by no means unusual to obtain positive darkfields even from dry papules of a secondary eruption. Condylomas in the lat primary and secondary stages yielded 90.7 per cent positive darkfield findings while mouth and throat lesions yielded 85.6 per cent positives, and cutaneous lesions 78.3 per cent. It was found that age of the patient has no effect on the proportion of positive darkfield results.

The increasing simplicity and trustworthiness of the skin tests for chancroid and lymphogranuloma venereum will inevitably raise the question as to an appropriate cross-check for the presence of these diseases in the presence of an undoubted syphilitic primary lesion. If the physician can realize that a positive chancroid, Frei or Lygranum test does not in the least modify the fact that the patient may have syphilis if he could be induced to do the dark field *first and the skin-tests afterwards if he can realize that the positive* skin tests do not necessarily mean that the conditions they reveal are actually part of the patient s immediate clinical picture then perhaps after a long, and probably painful process of education routinization of the chancroid and lymphogranuloma venereum skin tests may be encouraged

The ardor of the serologist in advocating the earlier recognition of a seropositive blood in the primary stages of syphilis as a substitute for a darkfield examination must be viewed with only qualified approval. The margin of error of the hypersensitive serologic test probably approaches or even exceeds that of the darkfield, and a crop of false positives in the one case is as likely to match a crop of false negatives in the other as is any other outcome of over enthusiasm It may then be insisted that properly performed darkfield examination within the exceptions previously and repeatedly described has great dependability There should be no hesitation on the part of efficient medical organization in the employment of darkfield examination and the acceptance of its result in the seronegative primary stage of syphilis. On the other hand even competent medical organizations would be well advised to view with conservatism the application of presumptive serologic tests to the diagnosis of primary syphilis. The practicing physician who considers that a patient has not had syphilis unless he has had a positive serologic test on the blood regardless of his darkfield findings, is a not infrequently encountered obstacle to continuous and effective treatment in the seronegative primary stage of the disease

Effect of Local Treatment.—The influence of local treatment in reducing *the efficiency of the darkfield examination is well shown by Driver s series of* 171 chancres, in which a positive result was obtained in 57 per cent. Of these 171 cases, however 90 gave no history of local treatment, and of these 81 per cent gave positive darkfields, while of 81 cases which had been treated locally before darkfield examination only 28.5 per cent gave positive results. Our own observations on this point, while supporting the general principle that "no treatment should be consistently and vigorously preached, tended to show that the fact of previous treatment of the local lesion does not make the darkfield useless. Of 17 chancres in treated patients, 11 or 71 per cent, *yielded positive darkfields Of the 11 patients with positive darkfields, 8 had* had local treatment including cautery and 3 had had arsphenamine and mercury The positive darkfields in the treated cases were obtained by repeated examinations after salt solution soakings.

Aspiration of Lymph Nodes —If the lesion itself after careful and repeated

examination by the technic given in Chapter III fails to yield a positive darkfield, aspiration of the adjacent lymph nodes should be done if they are sufficiently enlarged to be reachable (p 57) This procedure is of the greatest value in suspected chancres about the lips, mouth and throat. That it is effective in genital lesions is indicated by the fact that even with the older "dry" method which has been much improved by the injection of saline or distilled water before aspirating we obtained 50 per cent additional positives in 12 lesions otherwise negative to darkfield.

It cannot, then be too strongly urged upon physicians, or made too prominent a feature of educational campaigns, that the fresh untreated lesion is the one from which the promptest, most accurate diagnosis can be made, and at the same time the one which if it prove to be a chancre offers the patient the best hope of radical cure The methods by which this consummation may be brought about are specially discussed in Chapter III Systematic effort to wean the young man away from the prescribing drug clerk with his calomel powder the ready friend with his home-made acid cautery

Fig. 254

DIAGNOSTIC ERRORS IN 80 CASES OF PRIMARY AND SECONDARY SYPHILIS

The first diagnosis was	Cases.
Chancroid	10
Gonorrhea	3
Carcinoma or tumor	3
Furuncle	2
Eczema	2
Vincent angina	1
Tuberculous tonsil and gland	1
Herpes simplex	1
Coryza	1
Smallpox	1

or the physician who still "burns em off" is the modern preventive trend in the treatment of syphilis.

Eighty patients in Stokes and McFarland's series had seen physicians before they reached the authors. Seventy per cent had received correct diagnoses, and 30 per cent incorrect diagnoses. This showing, though good, is far from ideal, especially because many of the diagnoses were late rather than early

The Blood Serologic Reaction in the Diagnosis of the Chancre.—The average physician, confronted with a genital or other suspicious lesion and not equipped for a darkfield examination, may if his suspicions are aroused, take blood for a Wassermann test. In doing so he should clearly realize that so far as the earliest possible diagnosis of the lesion is concerned he is employing a method which is at its worst precisely at a time when the darkfield is at its best. He is, moreover deliberately sacrificing his patient a chance for complete "cure." The inverse relation between the two procedures is again shown in Fig 253 In a small series of cases such as this represents, the proportion of positive blood Wassermann reactions at the beginning of the second week is fortuitously high, and seldom averages above 35 to 50 per cent. Hoffmann believes the proportion of authentic positives not to exceed 35 to 50 per cent by the end of the second week. From this point on it increases steadily to 80 per cent or more at the end of the eighth week.

Serological Results in Primary Syphilis.—The advance in the sensitivity of serological tests is well illustrated by the increasing incidence of positive results being obtained in primary syphilis The Handbuch, in figures dating to 1910 gives 60 per cent positives by the eighth week and quotes Fischer as giving 80 per cent positives by the ninth to tenth week. The incidence of positives by the more recent tests such as the Kolmer and Kahn, yield as high as 75 to 80 per cent positives by the end of the second week with the Kolmer test, and 56 to 90 per cent with the Kahn test, certainly represents a tremendous advance in diagnostic effectiveness It is important, however to remember that the appearance of a positive test may be long delayed—in exceptional cases as late as 100 to 120 days after infection. Figures will differ as to whether they refer to date of infection or date of first appearance of the primary lesion and it is possible that some of the apparent advantage of present-day tests results from a difference in interpretation on this point.

The Serological Follow-up.—If the initial and repeated darkfield examinations are negative and the blood tests are reported negative, the patient should under no circumstances be considered as proved nonsyphilitic He must then at once be placed on the so-called "serological follow up to detect the development of the infection regardless of the characteristics of the lesion or the appearance or nonappearance of secondaries It is inexcusable at this stage in our opinion casually to begin the systemic treatment of a case because it "looks like syphilis, or to fail to follow it up by serological tests because it "doesn t look like syphilis If the examiner has been forced to give up hope of a positive darkfield and cannot utilize the local Wassermann he may begin local treatment of the lesion, but he must not begin systemic treatment short of diagnosis without full realization on his part and the patient s that it must be followed through in full as if the diagnosis had been made

It can at least be said that if treatment is begun without a diagnosis it should be followed through on a maximal basis as if the diagnosis had been syphilis The monorecidives and neurorecurrences which one observes as a result of any other practice are most unfortunate affairs

Frequency of Blood Serological Tests in Follow-up.—Since the purpose of the serological follow up is to obtain a positive result as early as possible, the tests should be taken at shorter intervals early in the course of the lesion and at longer intervals later A daily blood test on the darkfield-negative chancre is ideal but seldom practicable. A test once or twice a week until the lesion is six weeks old is usually possible in dispensary and hospital practice or with the cooperation of state or municipal laboratories If this requirement cannot be met, the age and general appearance of the lesion must be taken into account. In an older lesion the second test may be taken at a shorter and in a fresh lesion after a longer interval from the first visit. Blood serological tests on the fourth eighth, and twelfth week after the appearance of a lesion with negative darkfields can be regarded as an absolutely minimum requirement. We believe furthermore that one more test should be taken four month after the appearance of the lesion inasmuch as cases are occasionally known to have an exceedingly long secondary incubation period

Physical Examination Essential.—It should go without saying that the repeated serological tests should be accompanied by a periodic examination of the patient completely stripped in a good light The mucous membranes, anal region palms and soles should be given special scrutiny Inquiry should be made at the same time regarding the preroseolar constitutional symptoms,

particularly headaches, loss of weight, anorexia, malaise, and arthralgias. These symptoms often appear some time before eruptive manifestations, and

Fig. 255.

TONSILLAR CHANCRE (?). TONSILLECTOMY. CERVICAL ADENITIS. POSSIBLE ERRONEOUS INTERPRETATIONS DUE TO INCOMPLETE EXAMINATION

Girl aged nineteen years.

11/29/19 **Examined.**

Nose and Throat Specialist's Examination

Chief Complaint Tonsillitis, swollen glands.

10/15/19 **Tonsillitis, severe**

11/1/19 **Tonsillectomy (?)** Glands did not subside. No pain or tenderness.

11/29/19 **Otolaryngologist's Examination** (verbatim) "Small ulcer with pus, upper part of hard palate. Tonsils 3 (large) right. Large left stub with much induration. Soft plugs right marked granular pharyngitis mucopurulent material in nasopharynx. Nose and ears nothing of note. Gland, size of a walnut, right cervical region.

"Summary question of lymphosarcoma or Hodgkin's. Wassermann test to rule out syphilis. Does not resemble tuberculous glands. History of repeated attacks of tonsillitis each winter. General health good.

Transferred to Syphilologist when Serum Wassermann Reaction was Found to be Strongly Positive.

Dermatosyphilologist's Examination

Chief Complaint Positive Wassermann reaction and sore throat with glandular involvement.

11/30/19 Differential count negative.

12/2/19 **Syphilologic Examination** (verbatim) "Cervical adenitis described. Hair thinned. Small patches of depigmentation on neck. Across upper extremities, shoulders, and upper thorax faint maculopapular eruption, only visible by cross illumination. Apparently involuting roseola.

"*Genitalia.* Right labium majus, several small eroded papules and a large irregular ill-defined indurated plaque size of dime. Labia minora eroded.

Mucous membranes. Erosion of hard palate, darkfield positive for *Spirochæta pallida.* Mucous patch left anterior pillar.

General adenopathy.

Vaginal introitus intact.

"Genital lesions present one and one-half weeks.

DISCUSSION

1. The two examinations are paralleled and quoted verbatim to show the difference in point of view.

2. Persistent painless cervical adenitis associated with a throat or lip lesion should arouse a suspicion of syphilis and lead to an investigation by darkfield, gland aspiration, serological tests, and complete physical examination.

3. Specialists whose work is sharply limited to a particular region or group of structures are especially prone to overlook syphilis by missing its collateral manifestations. Every specialist should make a rapid general examination by a good light if he wishes to recognize the syphilis which passes through his hands.

4. This patient sustained a partial tonsillectomy for a probable tonsillar chancre, and her medical adviser proposed an excision of the glands, constituting the satellite bubo of her tonsillar chancre on a presumptive diagnosis of tuberculosis, because he overlooked the possibility of syphilis. The otolaryngologist did not place the possibility of syphilis first instead of last, because he did not see the skin and genitalia. He suspected lymphosarcoma or Hodgkin's disease.

5. The intact vaginal introitus does not prove a tonsillar chancre as against a genital chancre. Mere contact without consummation of intercourse may result in infection. The circumstances of the case and the cervical adenitis make a tonsillar primary lesion the stronger probability.

6. Many tonsillar chancres are operated on each year through failure: (1) To suspect cervical adenitis of being a satellite bubo; (2) to order a darkfield on an erosion; (3) to consider syphilis before diagnosing Vincent's angina; (4) to make a serological test on every patient with a bad throat, and (5) to inspect the skin by a good light in every patient with a bad throat.

may warn the patient to report for examination before the time set for the next blood test appointment. The patient should therefore be instructed to be on the lookout for them.

Follow-up by repeated serological tests deserves the widest application in the management of all types of venereal disease and of every lesion, genital or extragenital, which has aroused the slightest suspicion. Diagnostic knowledge has progressed far enough now to make it absolutely unjustifiable for any physician to give his patient a final diagnosis of chancroid until four months have elapsed from the time of appearance of the lesion. Suspended judgment during this time would increase the amount of early syphilis recognized from 15 to 50 per cent.

Serological Follow up in Gonorrhea and Extragenital Lesions.—This should also be applied to all patients with gonorrhea even in the absence of a genital sore. Friedman's method for the identification of *Sp. pallida* in gonorrheal pus and the identification of the intraurethral chancre masked by gonorrhea has been discussed (page 58). Systematic adoption of this procedure would identify at an early stage 10 per cent of syphilitic infections in which no history of onset other than that of gonorrhea can be obtained. Systematic application of serologic follow-up to lesions in the mouth and throat would, without question, quite transform our conceptions of the extragenital onset of syphilis and would nip many a tragedy in the bud.

CHAPTER XII

THE DIAGNOSIS OF EARLY SYPHILIS—THE SECONDARY STAGE

There is no sharp demarcation between primary and secondary syphilis, immunologically or even clinically speaking The statement that the average interval between the appearance of the chancre and the development of secondary manifestations is eight weeks must be interpreted with numerous reservations. On the one hand definite constitutional symptoms and objective signs of generalized syphilis of the nervous system may be recognizable within a week of the appearance of the chancre On the other hand, the chancre may have been healed for weeks before any cutaneous or constitutional symptoms appear As a third possibility probably not rare, both cutaneous and systemic evidence of the generalization of the infection may be entirely lacking. As high as 60 per cent of patients found to have syphilis in later life can give no history of secondary lesions of any description. The mere fact that a patient has lost no hair had no sore throat or cutaneous eruption and no constitutional symptoms following a genital lesion is not the slightest proof that the lesion was not the onset of a syphilitic infection.

The proportions of various manifestations of secondary syphilis observed *on admission* in 2209 patients in the Cooperative Clinical Group material was skin 81 1 per cent throat and mouth 36.3 per cent genital lesions 10.9 per cent central nervous system, symptomatic 1 7 per cent asymptomatic 8.2 per cent alopecia 7 1 per cent eye lesions 4 per cent visceral lesions 0.2 per cent. Only a part of the patients were examined (CSF) for asymptomatic neurosyphilis on admission, which explains the small proportion.

Diagnosis of Secondary Syphilis Now a Serological Problem.—In pre-Wassermann days the identification of the secondary eruption was a differential diagnostic problem for the dermatologist, and often one of the first order of difficulty With the introduction of the serological tests the diagnosis of secondary syphilis as the sequel of a primary lesion has become practically entirely a laboratory issue. It can be said with as much positiveness as is allowable in any phase of medical diagnosis that a cutaneous eruption, general in character developing in conjunction with the evolution of a suggestive genital lesion, is syphilis, if the Wassermann, at first negative becomes positive during the development of the eruption, and *remains so* without treatment. Nonspecific positive Wassermann results in pityriasis rosea, in tuberculids, and in atypical cases of the acute exanthemata, especially measles and scarlet fever are eliminated by the last proviso.

The high efficiency of the blood serologic tests in the identification of florid secondary syphilis does not, however, do away with the need for comprehension on the part of the physician of the essential characteristics of secondary syphilis. The presence of the secondary eruption may be the only sign to arouse the suspicion of the physician to the point of taking blood test. When the primary lesion is concealed or overlooked, as so frequently occurs in women, and not infrequently in men, or nonsyphilitic eruption is associated as coincidence with positive Wassermann or precipitation test due to intercurrent syphilis, or when treatment has weakened the test or made it temporarily negative, morphological differentiation resumes its full importance. Even when the association with positive blood serological reaction suggests the syphilitic nature

of an eruption, an alert clinician should not rest satisfied without a clear-cut understanding of the why and wherefore of the morphological diagnosis.

There is a noticeable tendency in the literature as well as in teaching to give the serological tests less than their just measure of confidence in florid secondary syphilis. Writers on the test take pains to guard themselves in allowing for the small percentage of untreated acute secondary cases with negative blood Wassermann reactions by needlessly cautious statements, and by endorsing the diagnosis of an untreated secondary eruption over the head of a negative Wassermann reaction, if its appearance seems to support the opinion. Such a point of view deprives the test of a well-deserved confidence. We have in our records and can recall many instances in which lichen planus and pityriasis rosea have been diagnosed syphilis because of a certain distrust of the repeatedly negative Wassermann reaction in the eruption stage. The dilemma in deciding the status of an early eruption becomes acute when as a result of ineffective treatment, lesions recur but the blood test remains negative (Fig. 256).

The Darkfield in Diagnosis of Secondary Syphilis.—Much time may be saved in waiting for serologic tests and clearing up diagnostic puzzles by developing a technic of darkfield examination of secondary cutaneous syphilids.

Fig. 256.

POSITIVE WASSERMANN TESTS IN FRANK SECONDARY SYPHILIS

	Per cent.
All cases as they come, treated and untreated	92 0
Some treatment, but not enough to cause complete involution of secondary lesions	95 7
Untreated cases	98 5
Cooperative Clinical Group, secondary stage	99 0

Superficial scraping of macular and papular syphilids to the point of exposing the lymphatics or with very slight exudation of blood makes it possible to identify *Sp. pallida* occasionally in the most unexpected fashion. Since the lesions used for this purpose are ordinarily on the glabrous skin, the confusion elements encountered in the darkfield examination of vegetative and eroded syphilids in the anogenital region can thus be avoided. The value of the dark field in the identification of secondary syphilis with a negative blood serologic reaction is also considerable. With proper precautions to prevent the confusion of saprophytic spirochetes with *Spirochaeta pallida* a diagnosis of syphilis can be made by the ensemble of the case plus the finding of the organisms, even without a chancre or history of exposure. In the series studied by McFarland and Stokes 7 such cases appeared in a total of 231. In 5 of them the presence of *Spirochaeta pallida* in lesions examined by darkfield was decisive of the diagnosis. Where genital secondary lesions of the condylomatous type are present, the experience of the Cooperative Clinical Group indicates that 90.7 per cent will yield positive darkfields with 85.0 per cent positives in mouth and throat lesions and 70.3 per cent positives in all cutaneous lesions including condylomas.

Diagnosis by Ensemble.—Diagnosis by the ensemble of the case is sometimes the last resort, and should in general be made after consultation if possible. Atypical eruptions of lichen planus and pityriasis rosea will furnish

the chief possibilities of error The mere combination of a genital lesion and an eruption, or an eruption with mouth lesions cannot be accepted as establishing a diagnosis of syphilis.

Secondaries, But No Primary.—One of the interesting and suggestive details of the study of early syphilis was the proportion of patients who although presenting obvious secondary lesions, had no evidence of a primary lesion at the time of examination and could give no history of one. Twenty-four per cent of the series of 231 cases including men and women, with all types of lesions, gave no evidence in history or examination of ever having had a chancre. The general bearings of such observations have been discussed in the preceding chapter and in Chapter I (asymptomatic carriers)

The Dermatology of Early Syphilis.—Figure 258 taken from McFarland and Stokes's series of 231 early cases, serves as an excellent introduction to the dermatology of early syphilis because it indicates the type of lesion which one must expect to encounter in dealing with the generalization of syphilis, and possibly why it is so often said by men working under unfavorable conditions that they never see secondary syphilis. The tendency to illustrate textbooks with wall paper syphilids—large papular pustular varioliform, annular rupial—is regrettable because it leads the student to expect cutaneous syphilis to be glaring and obvious, when in reality it is fugitive, inconspicuous,

Fig 257

HISTORY OF CHANCRE

	Per cent			
	Chancre.	No chancre.	Genital.	Extragenital.
Men	82	18	83	17
Women	56	44	64	36

and easily misinterpreted. The inconspicuous syphilids, in our experience many of which cannot be and were not seen by competent men under the average office lighting conditions, total 86 per cent of the entire group of secondary syphilids observed. The visible, obvious syphilids, which it is a pleasure to photograph and to present before a class, did not exceed 14 per cent of our group In fact, our group included examples even of the almost "extinct" macular follicular syphilid, which we were able to recognize under favorable lighting conditions.

Aids to Detection of Secondary Eruptions.—Of material assistance in identifying these difficultly visible early syphilids is the ability to observe the patient for the twenty-four hours following his first arsphenamine injection. This utilizes the therapeutic shock and confirms or negates the impression made on first examination. The physician who examines patients in a small room, in which he cannot secure distance and varying angles of illumination, who works by poor daylight or artificial light in the average dispensary night clinic, or first-floor office; or who gives his patient a first dose of arsphenamine and does not see him again for a week, cannot, with the best intentions, recognize much of the early cutaneous syphilis which passes through his hands. The male patient overlooks his eruption and cannot, therefore be relied on to bring it to the attention of an examiner In women, who may present no sign of a primary lesion to arouse suspicion, favorable lighting conditions for the recognition of the inconspicuous syphilids are particularly important. Wherever inspection is being made the basis for a recognition of venereal disease, as in industrial and military medicine, this vital consideration of proper illumination must be borne in mind if the best results are to be secured.

Vasomotor Factor.—The attempt to identify roseolas in cold rooms, especially if suspicion is already aroused to sharp pitch by the presence of genital lesion, may lead to serious mistakes through the misinterpretation of an accentuated marbling of the skin, the normal cutis marmorata, for a macular syphilid.

This is especially apt to occur in patients with "vasomotor skins," which express their emotional stress. Even a patchy follicular eruption can be momentarily suggested to the novice by causing the chilled or nervous patient to "goose flesh" locally by touching him here and there upon the skin of the flank and back. While these considerations rarely trouble the expert, the student may at times find himself on the verge of self-deception in his enthusiasm.

Racial and Sex Differences in Cutaneous and Mucosal Secondary Syphilis.—Early skin manifestations appear fewer in colored than white patients, being probably masked by pigment and fewer in colored women than white women or males of either race. Mucosal secondary lesions other than condylomas are more common (10 per cent) in white than colored patients. Condylomas (p. 535) are more frequent in women than men and the colored woman holds an unenviable record in this regard, these infectious lesions being 3.5

Fig. 258.

TYPES OF CUTANEOUS SECONDARY SYPHILIS OBSERVED

	Cases.
Macular	54
Maculopapular	25
Large macular	10
Grouped follicular	11
Papular	5
Corymbose papular	3
Psoriasiform papular	2
Grouped follicular and papular	2
Lichenoid miliary papular	1
Annular papular	1
Pigmentary follicular	1
Pigmentary papular	1
Papulopustular	1
Rupial	1

times as common as in the white male, 3 times as common as in the colored male and more than twice as frequent as in the white female (Cooperative Clinical Group).

MORPHOLOGY OF CUTANEOUS SECONDARY SYPHILIDS

Secondary syphilids combine five lesions with five attributes or qualities as follows:

1. *Lesions.* Macule, papule, pustule, "follicule," scar.
2. *Attributes.* Distribution, configuration, association, induration, indolence.

Color.—While the indolence of a lesion is to some extent indicated by the height of the inflammatory coloring and the admixture of chronicity due to pigmentation, color is relatively seldom a necessary element in the differentiation of syphilids. To be sure, the violaceous color of the eruption of lichen planus has weight at times, and the fawn-colored center and pink border of the annular lesion of pityriasis rosea is helpful in identification of this important lesion. But so much diagnostic error has arisen from the misuse of the "raw-ham" and "copper-colored spot" conceptions that, for a time at least, the mind of the student should be disabused of the notion that a colored plate or a colorful eye is in any way necessary or even trustworthy in the diagnosis of early syphilis.

No Vesicles in Adults.—An almost unexceptionable rule of thumb may be found for all practical purposes in the statement that if vesicles are an essential part of an eruption in an adult, *the lesion is not syphilis*

While vesicular syphilids in adults have been described, they are like diffuse syphilitic dermatitis and syphilitic erythema nodosum, rarities of the first order and not as yet entirely above dispute. For the average practitioner they certainly have no meaning at all in the everyday work of diagnosing early syphilis. It should be noted that the bullous syphilid of infancy is excepted.

Rules of Thumb on Distribution.—The early secondary syphilids, as may be expected from the distribution of the *Spirochaeta pallida* at the time they appear tend to be universally distributed over the surface of the body Certain syphilids show a tendency to localization expressed in Fig 259

Variations are numerous, and subforms of the various types, such as the annular papular and psoriasiform papular have distinctive little peculiarities of localization at times. For example, the following should be borne in mind

The papular phase of the macular eruption, if the two are combined, tends to appear upon the mucous membranes as mucous erosions, and on the palms and soles as papules.

The maculopapular eruption tends to be associated with condylomata at the anus and in the flexures.

Fig. 259.

LOCALIZING TENDENCIES OF EARLY SYPHILIDS

Type.	*Localization.*
Macular:	Flanks and abdomen, shoulders, upper arms, back, and chin
Papular	Same as macular, but with an increased predilection for face, palms, and soles.
Pustular	Face and scalp. The rupial and other severe types may be universal. This is the varioliform distribution.
Follicular	Back and extensor surfaces. Scalp (alopecia)

Annular secondary syphilids occasionally appear upon the face in white patients. They are much more common and of more general distribution in the colored patient.

The follicular eruption cannot appear upon the palms and soles because in these sites there are no hair follicles.

An involuting papular eruption tends to persist longest in areas of vascular stasis or congestion, provided they were included in its original distribution as in the case of the papular and pustular syphilid about the rosacea area of the face and on the dependent parts of the extremities (palms and soles)

A macular eruption is usually best seen just posterior to and below the axilla or over the shoulder

Early syphilids, in seborrheic persons, tend to be accentuated in the areas of predilection for seborrhea—the scalp presternal and interscapular regions.

Configuration.—Grouping of lesions and annular or ring-shaped configurations always bring syphilis into the differential diagnosis. While this is more especially true of late lesions, it is of very great importance in certain early syphilids. The clumping of lesions is best illustrated in the corymbose and the grouped follicular lesions. A corymbose lesion consists of a central large lesion, usually papular surrounded by a group of lesser satellites (see



Fig 260—A coarse macular syphilid. (Collection of Dr H W Stel agon.)



Fig. 261.—A small macular secondary syphilid. The photograph was taken by arc (ultraviolet) light which increases the distinctness of the eruption. It is seen with difficulty by daylight. The eruption had been overlooked, and the extragenital chancre diagnosed furuncle.

ing is, however a common characteristic of two other types of follicular lesions, the dermatophytid, and the tuberculid known as lichen scrofulosorum.

A special interest attaches to the follicular syphilid because of its demonstrated association with neurosyphilitic involvement. On the skin the follicular syphilid is produced by infiltration of the hair follicle. On the scalp this infiltration of the hair follicle is accompanied by loss of the hair producing the patchy moth-eaten alopecia of secondary syphilis (Fig. 345) Alopecia is more frequent in white females than white males, and twice as frequent in white as in colored females (Cooperative Clinical Group) Wile has shown that there are two types of alopecia, one of them due to the grouped infiltrative syphilid of the hair follicle, the other presumably to a lesion of the cervical sympathetic ganglia without direct involvement of the hair follicle itself



Fig. [illegible].—Remains of maculopapular syphilid the atrophic macular syphiloderm. The patient had syphilitic encephalitic process.

This highly interesting and important discovery may have important bearing on future work upon the mechanism of development of cutaneous syphilids.

The pustular syphilid is comparatively uncommon though more frequent in the Negro. A few pustules may form part of the picture of a papular syphilid about the nose and forehead. The typical pustule is indolent, often simply softened in the center and crusted over rather than actively inflammatory and pus containing, so that, unless a careful distinction is drawn between crust and scale, a pustule may be taken for a greasy psoriasiform papule. The giant pustular syphilid, for it is really such, is called rupia (Fig. 99) It is more common as a recurrence than as part of the original secondary eruption. The lesion is a cold, indolent ulcer whose crust through successive accretions from below as the lesion enlarges, heaps up into a lamellated pyramidal hardened mass of a conical or oystershell configuration

Residua and Scars.—The macular syphilid rarely leaves even the faintest traces. The scars of secondary syphilids of the papular type, when they develop, are the results of destruction of elastica by the lymphocytic infiltration in the corium and take the form of macular atrophy (Fig 262) Even very slight degrees of papular infiltration scarcely detectable as such clinically may give rise to this atrophy which however is one of the more unusual lesions. The majority of papular eruptions, even of an extreme grade, involute without leaving a trace, though increased pigment may persist for a time. The pigmentary syphilid, so-called (Figs. 446 447) is, properly speaking, the residuum of a papular syphilid, and consists of depigmented macules on a



Fig 263 —An unusual type of pityriasis rosea, simulating macular syphilid. Differential diagnosis in Fig. 270.

hyperpigmented base It will be considered among the cutaneous landmarks of latent and late syphilis.

Infectiousness of Cutaneous Syphilids—The dry uneroded early cutaneous syphilid is noninfectious so far as contact is concerned The pustular and rupial types are self-sterilizing so to speak. Macular and papular lesions which occur in flexures or crypts such as the axillary and inguinal folds, under the breasts or in the umbilicus, may erode and assume the characteristics and infectiousness of mucous lesions. In men a careful search of the scrotum and of the balanopreputial folds should always be made. (See Figs. 417 418 in the discussion of relapse Chapter XIII Identical lesions occur in florid secondary syphilis.)

The Lesions of the Mucosae and Mucocutaneous Junctions in Early Syphilis.—This important type, which is practically synonymous with the infectious lesions of secondary syphilis, included 58 per cent of 183 patients with secondary syphilids in McFarland and Stokes' series and 56.2 per cent in the Cooperative Clinical Group's 2260 patients on admission. Seventy-five per cent of the women and 64 per cent of the men in our series had lesions of this type, a proportion of women which is somewhat lower than the usual, possibly because routine speculum examinations were not made. Women present a much higher proportion of infectious lesions than men and colored women highest of all.

First among lesions of the mucous membranes should be mentioned syphilitic sore throat, a diffuse inflammatory involvement of the pharynx and tonsils, with extensions of varying degrees of severity into the naso-



Fig. 294.—The coarse macular exanthem of leprosy. The hands of this patient are shown in Fig. 485; the differential diagnosis in Fig. 271.

pharynx and larynx. The grade of inflammatory change may vary from the most trivial reddening with a sense of dryness, to extensive diphtheroid involvement with the formation of pseudomembrane and even of extensive necroses and sloughing. Tonsillar changes in syphilis are, however, more apt to be of the erosive type, the tonsil being swollen, red and boggy at the base, with a thin grayish or pearly exudate partially or completely covering the surface. Edema is usually marked and there is a striking accentuation of the lymphatic follicles, as in a follicular or granular pharyngitis. Extension into the larynx results in redness and edema of the cords, with corresponding impairment of function. Hoarseness can often be detected when no gross involvement of the pharynx is visible, and may serve as a valuable clue to an otherwise obscure infection. Complete aphonia lasting for weeks may occur with an abrupt onset and recovery at times suggestive of an hysterical origin.

An inspection of the vocal cords may at times be the only means of identifying the real nature of the trouble.

Mucous Patch.—The typical lesion of the mucous membranes in early eruptive syphilis is the so-called "mucous erosion" or mucous patch (Figs. 364 412, 428) This is essentially the homologue of a macular or maculopapular lesion on the skin whose surface has been eroded by the moisture and friction to which it has been subjected. Local irritation moisture, and trauma, which act as predisposing factors, tend to make these lesions appear about the surfaces of tongue, buccal mucosa, and lips. The typical mucous patch is slightly raised above the surrounding surface, very faintly inflammatory and presents a smooth round or oval central erosion covered by a flesh-colored to pearly or faintly grayish delicate membrane When this is removed the base is seen to be clean, flat, and of a flesh or pinkish color rarely with a tinge of yellow Mucous lesions are seldom less than 5 mm. in diameter and are frequently from 7 to 10 mm. in their greatest diameter They are comparatively painless. If the papule occurs on a constantly moving surface like the side of the tongue, the erosion or mucous patch may be irregular angular or stellate may be deeper and approach the ulcerative type. On the other hand if the papule occurs on the dorsum of a tough-surfaced structure such as the tongue, there may be no erosion, and the lesion remains a papule of a dark pink or reddish color flat, and smooth, but not eroded, and free from papillary markings. A group of them on the dorsum of the tongue may become confluent, forming a large smooth flat plaque.

Where secondary infection is a factor or the syphilitic infection is of unusual severity secondary mucous lesions may become ulcerative and cause scarring and destruction comparable to the effects of the rupial and pustular syphilids upon the skin Ulceration in mucous syphilids is an expression of lateness (recurrence) malignancy or of a precocious tendency to gummatous change The ulcerative mucous syphilid should be especially looked for in the pharynx and on the tonsil.

Genital Mucous Lesions.—Mucous syphilids about the genitalia are more common in women than in men, because the conditions about the female genitalia—moisture, friction, and a certain degree of irritation from detritus and saprophytic infection—are especially favorable to their development. They may occur upon the cervix as well as the more external moist structures. They may include macules, erosions, papules, ulcerations, condylomas—appearing either early in the generalization of the infection or later in infectious relapse, and all these types of lesions may appear successively in the same person. A yellow-based ulcer with fine pink striations is also recognized. It is important to realize that quite as typical a mucous patch may develop under the foreskin of the penis as on the labium minus or at the introitus, and that it may be fully as effective in transmitting the disease. Moreover a penile papule dry at the outset (Fig. 417) may be converted into a mucous erosion by the mere process of coitus, and serve as a source of infection for a healthy partner The special tendency to develop mucous lesions observed in prostitutes has many times been pointed out, and is the natural consequence of the combination of irritation and uncleanliness they so frequently present. That this single fact has the gravest meaning in the transmission of the disease is self-evident.

Evanescent Character—The evanescent character of mucous lesions deserves special emphasis. They may be here today and gone tomorrow *It is*

not at all impossible for a throat which on one examination presents no more than a mild angina, to be the site of a tonsillar or buccal mucous patch at an examination twenty four hours later A superficial erosion may become almost unrecognizable even without treatment in the course of two or three days. Two or three weeks is, however a much commoner life for this type of lesion. The evanescence combined with the painlessness of the lesion explains that often emphasized but too little appreciated statement that the patient who has syphilis may never present a symptom to lead him to consult a physician or to warn him that he is dangerous to others.

Condyloma.—Condylomas (Figs. 300–303) are essentially vegetative hypertrophies of the cutis and epidermis, which are not by any means distinctively venereal or syphilitic in origin. Superficial erosions about the anal and genital regions in particular may become hypertrophic no matter what may have been the original cause of the erosion. The condyloma as such is not, therefore, distinctly venereal. Every transition stage from mucous patch to enormous cauliflower vegetations may be found in syphilis. Even the primary lesion of syphilis itself may conceivably present the appearance of a papule which following erosion has undergone vegetative hypertrophy and may then be diagnosed a venereal wart.

The flat wart or condyloma latum is usually syphilitic, as distinguished from the pointed or filiform papilloma or nonspecific condyloma acuminatum. The typical condyloma latum begins as a raised, slightly mammillated or smooth papule, with a moist eroded surface. As the hypertrophy progresses, the lesion stands higher above the skin and usually mushrooms out somewhat over a thick short stalk or forms a button-like plaque with a smooth surface. It rarely becomes pedunculated. Linear condylomas may develop in fissures. Neighboring lesions may become confluent, forming soft spongy masses with a cauliflower structure obscured by the erosion of the surface and by a thin grayish pellicle of exudate similar to that covering the mucous patch. Necrotic débris, rich in saprophytic organisms, and especially *Spirochaeta refringens* easily collects and obscures the bacteriological picture. The pointed variety (condyloma acuminatum) is much more commonly associated with the discharge of chronic infections of the genito-urinary tract, especially of gonococcal origin. The surface of this type of lesion is more papillomatous and even fimbriated, and pedunculation is not unusual. Both the broad and the pointed condyloma may be confused with the ordinary wart produced by a filtrable virus, which is so common upon the hands and fingers. When this lesion develops upon the genitalia (Fig 304) while it remains fairly dry and often has a hard surface, it assumes a mammillated or cauliflower aspect that may suggest a venereal condyloma. It has, in fact, been recently contended that the two are identical.

Condylomas rarely appear about the oral mucous membranes and mucocutaneous junctions or on the male genitalia. On the other hand, they are common about the female genitalia, appearing in the folds about the labia and on the inner aspects of the thighs and groins. Transition stages from the dry papular lesion of the skin to the moist cauliflower vegetation can be seen in such sites. Under conditions of congestion, irritation, and filth they may reach enormous size, entirely obscuring the surrounding structures. The entire vault and floor of the vagina may be transformed into a mass of condylomatous vegetations. In both men and women the anal region is a favorite for condylomatous hypertrophy of papular lesions.

Darkfield Diagnosis of Vegetative and Mucous Lesions.—The diagnosis of the mucous and vegetative lesions of early systemic syphilis, like the diagnosis of the primary lesion and the secondary eruption has been greatly simplified by modern laboratory methods. The darkfield in particular is a useful aid. Of twenty four darkfield examinations taken on mucous patches and condylomas in McFarland and Stokes series, 23 yielded positive results. Here again treatment in 8 cases did not prevent our obtaining a positive darkfield, and the darkfield was negative in only 2 treated cases. Positive darkfield examinations were obtained on 90 " per cent of condylomas and on 85 6 per cent of mouth and throat lesions in the Cooperative Group series. While the bacteriological picture in lesions deep in the mouth or throat must be interpreted by an expert and may be deceptive, lesions about the lip are usually cleaner and if spirochetes are abundant after wiping the lesion, as they usually are, the diagnosis is practically established

In lesions both of mouth and anogenital region, the morphologically similar *Sp. microdentium* can be cause of confusion. In recently observed case, *Sp. pallida* like organisms were found on the slightly verrucoid surface of superficially eroded pigmented nevus. Simultaneously the patient developed positive blood serologic test which subsequent study indicated was post-vaccinal. The gravity of the risk of not treating this particular patient, nd the confusion elements in the findings led to the use of ten-week intensive arsenotherapy during which the serologic test became negative, but the pallida-like organisms required two weeks (six mapharsen injections) for disappearance The patient is now clinically and serologically normal.

The condyloma must be thoroughly cleaned and even vigorously abraded or the top sliced off before examination if the result is to be trusted, but the serum usually so swarms with typical *Spirochaeta pallida* that there is little room for doubt as to the diagnosis. The finding of an occasional spirochete in mouth or genital lesions cannot be trusted when unsupported by other findings.

THE DIFFERENTIAL DIAGNOSIS OF EARLY CUTANEOUS SYPHILIS

The differential tables here given aim t strike salient points and to give rounded picture of differences, which ma occasionally slight special point on which the hole story in given



A B

Fig 243 —Macular seborrheic dermatitis in its t typical localizations bet een the scapulae and over the sternum. Not the tendency to confluence The lesion have faint, greasy yellowish scale

case will depend. T make the illustrations nd the differentiations cover everything that may ever in any aspect simulat syphilis, or which syphilis *itself* may ever *simulate*, ould require text-book of dermatology and an atlas of large proportions. Only experience makes the complete differentiation and furnishes the background for the indispensable though often abused diagnostic instinct which marks the adept.

Macular Syphilids

Macular Lues II and Macular Seborrheic Dermatitis.—In seborrheic persons these two conditions may coexist, and the diagnosis of secondary syphilis be entirely overlooked if merely the skin be relied upon for clue (Fig 206) For this reason it is essential t carry through the com-

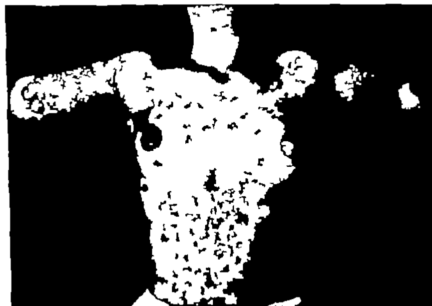


Fig. 206.—The seborrheic mask of secondary syphilis. A macular secondary syphilid assuming the characteristics of seborrheic dermatitis hen superposed upon seborrheic base. (Collection of Dr Grover Wende.)

Fig. 207

MACULAR SEBORRHEIC DERMATITIS	MACULAR LUES II
Predilection for nose, cheeks, postauricular presternal, and prescapular regions, axillae and groins.	None on face (except mottled chin"), least often marked on front of chest.
Rare in flanks and on shoulders.	Most common in flanks and over shoulders.
Fine yellowish greasy scale.	N scale Lesion pink, not yellowish (Maculopapular syphilids may scale.)
Tendency to become confluent in the larger folds.	Remains discrete.
May find minute vesicles, or lesions may become eczematous.	Never vesicular no oozing or crusting.

plete examinat ion on patients who present this type of seborrheic dermatitis in order not to miss evidence which may be present on the genitals, palms, soles, nd mucous membranes (Figs 265, 266).

Macular Lues II and Tinea Versicolor.—Tinea versicolor is rather common parasitic

Fig. 208.

TINEA VERSICOLOR	MACULAR LUES II
Usually large patches and geographic areas with scattered peripheral islets.	Discrete macules, no large patches.
F wn yellow or brown tinge.	Pale pink, not yellow or brown.
Confluent tendency marked.	N confluence. Lesions discrete.
Scale fine, furfuraceous.	No scale.
Papular lesions very rare.	Some papular elevation, slight but definite, may be present.
Ringworm fungus easily found in scales on digestion with 20 per cent KOH.	No ringworm fungus.
No adenopathy or constitutional signs.	General adenopathy and concomitant signs.
Months or years duration.	

Fig. 209

PROBABLE CHANCRE OF THE GUM, SATELLITE BUBO TREATED AS PHLEGMONOUS, HEADACHES MISINTERPRETED. SECONDARY ERUPTION ALMOST UNRECOGNIZED BECAUSE OF ARTIFICIAL LIGHT. HYMEN INTACT. FIANCÉ INFECTED BY ATTEMPTED FORCED COITUS.

Female, aged eighteen, school-teacher

6/21/16 Entered Clinic.
Chief Complaint. Infection right side of neck.
Thickening right lower jaw two weeks' duration.
Crown removed by dentist.
Adenitis incised and drained.
Rx shows abscess in front of first right lower molar.
Lesion described as swelling of jaw 4 inches in diameter.
8/19/16 Quinsy (?) and drainage of abscessed gland in neck.
10/7/16 Severe headaches began three weeks ago. Much orse at night. Slight delirium. Slight anemia. Hemoglobin 68 per cent.
Blood W ssermann reaction negative.
General examination negative.
Given KI and iron and observation d-vised.

1/5/17 Sent to Dermatologic Section for Acne. Seen by artificial light. Diagnosis of seborrheic dermatitis was made. In Carrying Through the Routine Complete Dermatologic Examination, Even Though It Seemed Unnecessary three large condylomata were found between the labial folds. Inspection of the skin by daylight showed faint macular eruption probably involuting, ith few grouped follicular lesions on seborrheic base.
Blood Wassermann reaction strongly positive.
Three weeks before, the patient fiancé had attempted forced coitus. On examination the hymen as intact. Patient warned t notify fiancé of danger of infection. Two months later the patient received letter from fiancé stating that he had developed signs of infection and was about to begin treatment.

Discussion

1. It is difficult to decid from the incomplet histories taken by various departments whether the swelling of the jaw with the associated phlegmon was the primary lesion ith its satellit bubo or whether the quinsy with "abscessed gland" marked the onset of the syphilitic infection.

2. Th misinterpretation of the satellite bubo of the headaches, and of the character of the eruption when seen by artificial light will illustrate how easily an extragenital infection, or any syphilitic infection in woman, may escape recognition even by well-trained clinicians.

3. It is impossible to decid th source of this patient's infection—whether from dental instruments, from utensils, or from personal intimate contact. The personality of the patient excluded perversions.

4. The time intervals suggest that the early secondary eruption may have been overlooked in the examination of 10/7/16. It was involuting on 1/5/17.

5. This case further illustrates how complet must be the dermatosyphilologic examination if mistakes are to be voided and how inexcusably inadequat are the routine office examinations with exposure only of such portions of the body are complained of frequently under unsatisfactory lighting conditions.

6. The infection of th fiancé is point of unusual interest. An intact hymen is not necessarily evidence that an infection extragenital. The time relations in this case make the oma the source of the man infection.

Fig. 270.

PITYRIASIS ROSEA MACULOPAPULAR TYPE	MACULOPAPULAR LUES II
Fawn yellow color over pink.	Pink color
Long axis of macules and papules in lines of cleavage.	Axial tendency absent or slight.
Slight crinkle and suggestion of annular lesions.	May be slight atrophic crinkling, but it follows the lesions.
Retiform network and some confluence.	Macules and papules remain discrete.
Pseudovesicles occasionally seen (rare)	No vesiculation.
Prodromal lesion (primitive plaque) may be found.	No prodromal lesion.
No mucous membrane lesions.	Mucosal and other concomitant lesions.
Limited to trunk and upper arms.	Look for palmar papules.
N general adenopathy or constitutional symptoms.	Often general adenopathy

Fig. 271

MACULO-ANESTHETIC LEPRA	MACULAR LUES II
Common on body	None on face (except mottled chin"), rare on extremities.
Lesions tend to be large, coarse, obvious, blotchy and scattered.	Lesions small, faint, close-set.
Tend to deeper brownish-pink or purplish.	Faint pale pink.
Definit infiltration common.	Slight edema, but palpable infiltration (except in definite papules) rare.
Persistent, lasting months or years.	More rapid evolution, over in one to three months.
Sensory changes and evidence of trauma on anesthetic parts.	N sensory changes.
Enlarged and painless ulnar nerves.	N ulnar nerve changes.
Syringomyelic hands.	No changes in hands.
Trophic disturbances and bullae.	N trophic disturbances.
Nasal smear shows acid-fast intracellular Hansen bacilli.	Nasal smear negative.
No mucous or genital lesions.	Concomitant mucous and genital lesions.

Fig. 272.

MEASLES	MACULAR LUES II
Prodrome of fever coryza, bronchitis, photophobia, and conjunctivitis.	No systemic symptoms unless fever typhoid type, and sore throat.
Koplik spots on mucous membranes, small punctate bright red with minute blue centers.	No Koplik spots; they do not resemble mucous lesions.
Adult patients usually very sick.	Adults usually little affected, up and around.
Eruption maculopapular with confluent tendency forming crescents.	Macules discrete.
Appears first on face, abundant in that region.	None on face unless few papules or "mottled chin
Eruption develops rapidly; two to three days.	Eruption evolves slowly matter of two to three weeks.
Lesions florid to dark red nd even hemorrhagic.	Lesions pale pink, never hemorrhagic.
Desquamation fine, furfuraceous, begins in five to seven days.	No desquamation.
Course run in tw eeks.	Course run in four eeks to three months.

disease of the skin, due to ringworm fungus, *Microsporon furfur* The lesions suggest seborrheic dermatitis more than macular eruption. The sites of predilection are the thorax, shoulders, and back.

Pityriasis Rosea and Maculopapular Lues II.—Pityriasis rosea is an eruptive disease of the skin, of unknown cause characterized in about 27 per cent of the cases by the appearance of

Fig. 273.

ROSE SPOTS OF TYPHOID FEVER	MACULAR LUES II
Usually sparse punctate, sharply defined, and scattered.	Lesions usually abundant, more closely set, resembling marbling of the skin (cutis marmorata).
Color lively pink or even red. Often darker central, even hemorrhagic point.	Pale pink, often scarcely visible, uniform, fades into skin.
Most abundant over abdomen.	Most abundant, flanks, shoulder back.
No other cutaneous or mucosal lesions.	Look for mouth, genital, palmar plantar lesions, and alopecia.

Fig. 274.

MACULAR TOXIC ERYTHEMA	MACULAR LUES II
Angina apt to be cut severe streptococcal type, much edema, even membrane Strawberry pharynx.	Angina milder more chronic accompanied by mucous lesions in mouth.
Fever high, patient apt to be quite sick.	Fever slight or septic, patient seldom ill.
Eruption abundant, rather florid, tends to confluence more abundant on the extremities, suggest measles in color may be hemorrhagic or punctate, and scarlatiniform.	Eruption usually scanty pale, confluence rare. Most abundant flank, shoulders never purpuric, punctate, or scarlatiniform.
Course short and acute two to seven days.	Course indolent prolonged, matter of weeks.
Desquamation occasionally	No desquamation (unless scaling of papules)
No general adenopathy	General adenopathy frequent.



Fig. 275.—The papular phase of a maculopapular syphilid, best seen in the anterior axilla and flank.

prodromal lesion, followed after an interval of five to fifteen days by an outbreak of similar lesions over the trunk and upper portions of the extremities. The prodromal lesion is spoken of as the "primitive plaque." It is usually an oval or ringed patch with a slightly raised faintly scaling

A B

Fig. 276.—A, Small papular syphilid. Some of the lesions are follicular. Slight scaling produces the whitish sheen on the penis. B, Lesions in A, natural size.



Fig. 277.—"Slow smallpox." A papular secondary syphilid of the palms, diagnosed variola. Note the collarets of scales about many of the lesions. For differential diagnosis see Fig. 294.

pink border and a fawn-colored slightly scaling center The annular lesions of the subsequent eruption resemble it to some extent, but are smaller The typical annular lesion of pityriasis rosea



Fig. 278.—A shotty papular syphilid of the soles. Such lesion is almost diagnostic except during outbreaks of variola.



Fig 279—Scattered papular syphilid of the soles, the only lesions presented by the patient, and nearly overlooked through failure to remove the shoes and stockings in preparing for examination.

can scarcely be mistaken for anything else by one who has once seen it, the differential difficulties being confined largely to the aberrant types. The pink border and the peculiar cigaret-paper crinkle and fawn color of the center are very characteristic (Figs. 263, 290-292). Pityriasis rosea

lesions have peculiar trick of rranging themselves ith their long axes in the lines of cleavage of the skin, especially over the upper back and flanks, which is sometimes almost sufficient for diagnosis. The differential importance of this eruption is considerable for it is repeated beto oc



Fig. 290 —Typical papular palmar syphilid associated with preponderantly macular eruption.



Fig. 291 —A typical corymbose papular lesion. For other corymbose eruptions see Figs. 330, 431

casionally accompanied by false positive blood Wassermann reactions, by the older technics, and may also occur in patients ho have had syphilis, giving the impression of seronegative relapse. The condition has ide range of eruptive manifestations which bring it into differential

consideration repeatedly and highly typical forms may be quite puzzling t the inexperienced. The course of the eruption lasts bout six to ten weeks in the average case, and ends in spontaneous recovery There may be some itching but no associated general symptoms, or adenopathy

Macule-anesthetic Leprosy and Lues II.—Leprosy while not common disease is singularly often confused with syphilis. In fact, it wears the mask of syphilis more often than any other disease, in our experience and rarely escapes at least one diagnosis of syphilis before it comes t recognition in this country Part of the confusion arises from the frequency of false positive blood Wassermann reactions under the older technics, which has not yet been done way with by the modern serological procedures. Other aspect of the objective differentiation are dealt with under papular and nodular syphilids and alopecia. The nasal smear and the examination for sensory changes will always be useful check on the dermatological findings if even the slight est suspicion presents. Enlarged and insensitive ulnar nerves, enlargement of the nipples, and the bluish syringomyelic hands and traumatized feet, hands, and knees (anesthetic areas) should always be searched for The differential scheme here considered is that of the "leprous exanthem, but the macular lesion may occur late (Fig. 264).

Fig 291.

PSORIASIS	PAPULAR LUES II
Nearly always involves one or more of the following regions, scalp, elbows, knees.	Rarely affects elbow or knees and usually pustular in scalp.
Predilection for extensor surfaces.	Predilection, if any for flexors.
Polymorphic. Tendency to form large confluent patches and gyrat and geographic contours.	Lesions usually discrete one type
Eruption and elementary lesion usually florid red.	Lesions usually duller brownish red.
Scale bundant imbricated, silvery platelike less easily detached.	Scale scanty flakes off easily does not accumulate
No induration other tha that imparted by resistance of scale	Marked shotty induration.
On curetting off the scale and lightly abrading the surface of the papule minut multiple hemorrhagic points ppear representing the tops of the capillary loops	On curetting off the scale and abrading the papule diff se bleeding nd no visible capillary points are seen. Only serous exudat is obtained at times unless the abrasion is carried much deeper than in psoriasis.
Palmar and plantar lesions usually scale more abundantly No induration. Nail changes common.	Palmar and plantar lesions shotty slight peripheral collarette of scales, nail changes rare.
No scars	No scars in early syphilids, slight atrophy or scars in recurrent and lat lesions.

Measles and M cular Lues II.—It has been source of some surprise to us to not that this error is not so extremely infrequent. The cases which have seen merely express the low index of suspicion toward syphilis which still prev ils in verage practice An axiom hich ill aid in preventing confusion of syphilis with exanthemata is thi if an eruption is slow and takes eek or t t go through the changes which it should in twenty-four t forty-eight hours, take Wassermann test, nd look for syphilis.

Typhoid Fever and Macular Lues II.—While this confusion is not common, it none the less occurs. A patient, after several weeks in bed ith rose spot on the bdomen, and septic temperature and mental stat recovered and was leaving the hospital. He was seen by particularly alert man be passed through the hall, nd the slight lopecia of the sides of the scalp noted at glance The physician had the presence of mind t stop the patient and on further examination the syphilis as identified.

Macular Toxic Erythema and Macular Lues II.—Following streptococcal sore throats and tonsillitis, and occasionally after intestinal infections, macular eruption of an evanescent type may ppear hich may be cause of concern, though rarel source of actual error in diagnosis

Drug Eruptions and Macular Lues II.—The foregoing considerations (Fig 274) also pply t the large group of macular drug eruptions.

PAPULAR SYPHILIDS

Psoriasis and Papular Lues II.—This, fortunately is not common source of diagnostic error although psoriasis in syphilitic patient may t times present some puzzling features.

Fig. 283.

PITYRIASIS ROSEA, PAPULAR TYPE	PAPULAR LUES II
Rare on face and below elbows or knees.	Common on face.
No palmar or plantar lesions.	Palmar and plantar lesions frequent.
Axial arrangement of papules in lines of cleavage.	No axial arrangement.
No induration.	Definite deep shotty induration.
Annular lesions common in mixed types with fawn-colored cigarette-paper crinkled centers and pink borders.	Rarely any annular lesions. All one or all the other (unless in negroes).
Prodromal primitive plaque.	No prodromal lesion.
No mucosal or condylomatous lesions.	Mucosal and condylomatous lesions frequent.
No genital lesions.	Genital lesions frequent.
No general adenopathy.	General adenopathy frequent.

Fig. 284.

ARSENICAL KERATOSES	PALMAR PAPULAR LUES II
Diffuse keratotic thickening often present.	Sometimes diffuse infiltration but little keratosis. Fleshy deep induration or edema.
Miliary hard, horny raised papules.	Larger flat indurated thickened papules, but seldom really horny (exceptions in lues cornée, see Fig. 841).
No scale.	Peripheral collarette of scale often present.
Crateriform depression in many papules with central horny point or spicule.	Surface smooth, usually no pit or depression, no spicule.
No arciform configuration.	Marked tendency to arciform configuration in late lesions.

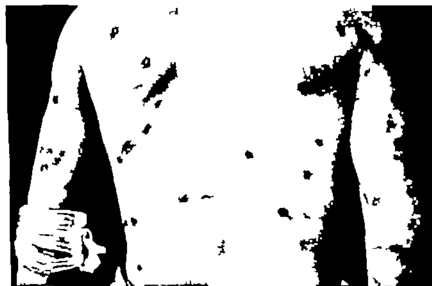


Fig. 285.—The psoriasiform secondary syphilid. Note the appearance of induration and the scanty scale as compared with Fig. 286. For differential diagnosis see Fig. 282.

Pityriasis Rosea, Papular Type, and Papular Lues II.—Most eruptions of pityriasis rosea involve both papular and annular elements, but one occasionally sees florid papular type which is quite difficult at first glance to distinguish from syphilid. The primitive plaque may be entirely absent in these cases. While the distribution of pityriasis rosea rarely involves the face,



Fig. 286 —Lesions of psoriasis, showing the greater superficiality and more conspicuous scale (See also Figs. 487 488.)

the lesions may occur on the face in children and in particularly severe outbreaks in adults (Fig. 290). I certain epidemics of pityriasis rosea the type form of the eruption may vary considerably from those described For example even i the adult, many of the lesions may appear on the face and neck, or large proportion of them may appear below the elbow and knees, leaving only an



Fig 287 —Papular psoriasis of the soles.

occasional though often typical lesion on the trunk to identify the process. I such cases axial distribution becomes unimportant, and the lack of induration, the fawn and pink color the cigaret-paper scale and annular form of occasional lesions, with the history of prodromal lesion, become the chief differential criteria. It must not be forgotten, moreover that pityriasis rosea may occur in patient ith syphilis.

Variola and Papular Lues II.—A severe papular syphilid may suggest quite decidedly the papular stage of variola, and in times of epidemic serious mistakes may result from the isolation of such persons in pest houses. The resemblance of the papular syphilid to variola is less marked



Fig 298.—Papular psoriasis of the rists and palms. The pitting of the nails often assists in diagnosis (see Fig. 299)

than is that of the pustular syphilid, but the following differentiation is important. In case of doubt it is advisable t isolat the patient pending Wassermann test and observation of the evolution of the lesions, but under no circumstances should such patient be placed among other



Fig 299.—The fingernails in psoriasis. The pitting of the nails of the middle and little fingers is especially characteristic

variola patients in smallpox hospital until the matter is decided. It is equally essential to keep under control the patient with varioliform syphilid for t least the week quired for full observation (Fig 332)

Pityriasis Lichenoides Chronica and Papular Lues II.—While this is comparatively rare condition, some cases may so perfectly mimic syphilis as to deceive even experts. Such case is shown in Fig 293. The cause of the group of dermatoses of which this condition is a member (parapsoriasis) is unknown. *They are all highly resistant to treatment of any kind and do not* respond t treatment for syphilis. The residual pigmentation hich follows the lesions may produce excellent imitations of syphilitic leukoderma (Fig 293) The Habermann syndrome (pityriasis lichenoides et varioliformis acuta) also strikingly resembles a papular varioliform syphilid, but is quit rare.

Lichen Planus and Papular Lues II.—Lichen planus is a cutaneous disease which, in some respects at least, bears striking resemblance to secondary syphilis. The distribution of the lesions is comparable t that of syphilis—over the trunk, arms and legs, in the mouth, and on the genitalia. The eruptions are papular and there is lichenoid syphilid which imitates them almost to

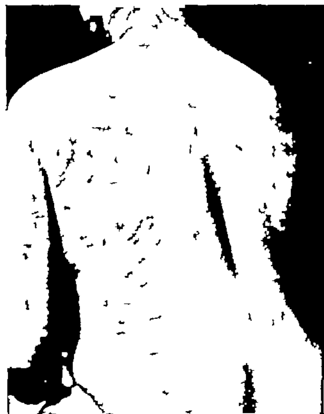


Fig. 290 —Papular pityriasis rosea. Not the tendency to distribution i the lines of cleavage of the skin. For differential diagnosis see Fig 293.

perfection. Annular lesions are not uncommon and upon the genitalia may be highly deceptive Lichen planus respond therapeutically t both arsenic (other than arsphenamine) and mercury and to the latter drug by mouth in doses and at rat which is not unl ke the response in syphilis, though somewhat slower Lichen planus gives rise in rare cases t follicular eruption, and at times to lesions on the palms and soles and bout the ankles hich suggest the keratodermic syphilids. W have even seen hypertrophic lichen planus on the penis simulat rather dry and verrucous condyloma (Fig. 302). There is even, as we have said, cutaneous reaction to arsphenamine which imitates lichen planus. It is evident, therefore that the physician ho is likely t deal much ith syphilis should familiarize himself with the eruptions of lichen planus, for w have seen it being burned t the treatment room under diagnosis of serologically negative syphilis in clinics of considerable size and have seen numerous vexations and embarrassing blunders from misdiagnosis in privat practice. A large part of the diagnosi of lichen planus under all circumstances rests on the identification of the elementary lesion, hich, fortunately is very



Fig. 291.—Psoriasis (elbow) and pityriasis rosea in the same patient.



Fig. 292.—Close-up view of typical lesions of the annular type of pityriasis rosea showing the cigaret-paper crinkle and scaling center. The peripheral portion of the lesion is pink, the center fawn colored.

characteristic, and which can usually be found about the wrists, over the shoulders, or on the forearms. The condition differs sharply from syphilid in being intensely pruritic, and much scratching usually results, with the development of characteristic papules in the scratch marks. Further



Fig 293.—Arsenical keratoses, unusually abundant. For differential diagnosis see Fig. 284.

differential considerations involving lichen planus are discussed under genital and mucosal lesions (Figs. 392, 393, and Chapter XV) There is, moreover lichen planus-like eruption occurring under arsphenamine treatment (p 422) which may cause confusion if misdiagnosed as syphilitic relapse (perhaps seronegative)

Fig 294.

VARIOLA (PAPULAR STAGE)	PAPULAR LUES II
Epidemic or exposure history	Not epidemic.
Sharp febrile prodrome with high fever backache, etc subsiding just before eruption ppears.	No brupt febrile prodrome or afebrile interval Fever and backache if present accompany lesions from the start, and persist.
Eruption rapid in onset, first lesions on face and wrists.	Eruption more gradual in onset, scattered more over face nd trunk.
Crop of lesions much al ke i age, size and shape	Lesions all ages, more variable in shape
Papular stage quickly passed, two to three days observation shows vesicular and pustular stage.	Papule slowly increased in size with little change in morphology Scale not crust, appears lat in course.
Areola bout trunk lesions.	Indolent, no areolæ.
Palmar and planta lesions may be hemorrhagic	Palmar and plantar lesions not hemorrhagic.
Mouth lesions acute, elevated, excoriated papules.	Mouth nd genital lesions indolent erosion.
	Concomitant evidence of syphilis. Isolate hile in doubt.

The Papulonecrotic T berculid and Lues II.—The differential diagnosis of tuberculids and syphilid is considered from the general standpoint in connection ith the landmarks of both diseases on the skin (Figs 351–357) It depends primarily upon the recognition of the essential lesion of the papulonecrotic tuberculid, hich is papule or in the earliest stages of its development, deep hemorrhagic vesicle that later develops necrotic central plug The plug hardens, and on separation leaves central pit, which later becomes the st of varioliform scar The

two tuberculids most likely to be confused with the papular syphilid are the papulonecrotic tuberculid of the face and that of the fingers. The former spoken of by some as acnitis, is illustrated in Figs. 303, 361 and the latter called folliclis, is shown in Figs. 312, A, B. Some morpho-



Fig. 295.—Pityriasis lichenoides chronica (Juliusberg) rather rare eruption easily confused at first with secondary syphilis. The dark macules in the picture are brownish-red papules, copper-colored spots, and pigmentary remains. For differential diagnosis see Fig. 296. (Collection of Dr William Allen Pusey.)

logically typical acnitis is not tuberculid, but may respond t arsphenamine. It is not at all uncommon for papulonecrotic tuberculid of the face t be treated as syphilis, and if arsphenamine happens to be employed, as as noted in discussing nonspecific treatment effects, the response may seem to clinch the erroneous diagnosis (Fig. 361).

Fig. 296.

PITYRIASIS LICHENOIDES CHRONICA	PAPULAR LUES II
Generally exempts the face.	Face and trunk.
N palmar and plantar lesions.	P lmar and plantar lesions frequent.
Little on extremities below elbows and knees.	Lesions frequent below elbows and knees.
Elementary lesion flat papule, flush with the skin or slightly raised with shiny surface showing no signs of scale until stroked ith curet (invisible scale).	Scaling more abundant, loose and self-detaching.
No definite induration.	Definite shotty induration.
Lesions of all ages and stages of evolution from macule to pigment.	Lesions more crop-like and of uniform type.
Extreme chronicity and resistance to treatment.	Definite progression two to six months' course.

Folliclis is less often mistaken for syphilid than is acnitis. It is less conspicuous, less acute



Fig 297—Lichen planus in young athlet who, although Wassermann negative, was refused as volunteer for the army on the ground that he had syphilis. Note the annular lesions, most often found about the wrists. This patient thigh is shown in Fig 298 The eruption is of distinctly purplish color Lichen planus furnishes some of the most deceptive imitations of syphilis, nd, moreover clears up under arsenic (but not arsphenamine) nd mercury (see Fig 302)



Fig 298.—The typical elementary lesions of lichen planus on hich the differential diagnosis from syphilis often depends (see Fig. 302) Note the polygonal, flat shiny papules. The glint on the surface is produced by the reflection of light, for there is no scale



g 299 —Annular lesions with trophic scarring produced by chronic lichen planus on the leg An annular lesion can be seen near the ankle.

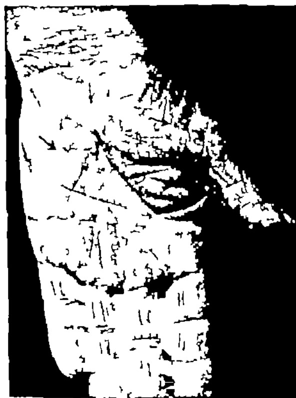


Fig. 300.—Lichen planus of the palm.



Fig. 501.—Lichen planus of the soles. This woman had received the diagnosis of syphilis. The diagnosis must be made on the remainder of the eruption and collateral evidence.

Fig. 502.

LICHEN PLANUS	PAPULAR LUES II
Rare on face, palms, and soles. Almost never occurs on scalp.	Relatively common on face, palms, soles, and may be pustular in scalp.
Characteristic elementary lesion (Fig. 498) flat polygonal papule with fatty or steely sheen or glint.	Elementary lesion an oval or rounded papule with rounded surface or hemisphere contour
No induration.	Marked deep induration.
Papular lesions small, 2 to 5 mm.	Papular lesions larger 5 to 15 mm.
Tendency to confluence.	Little or no tendency to confluence.
Specially characteristic lesions may be few	Lesions quite uniform in type.
Intense itching.	No itching or very slight (psoriasiform type)
Violaceous livid color with hyperpigmentation.	Brown red or "ham" color
Lesions appear in scratch marks.	No such tendency
Annular papular and umbilicated papular lesions not unusual. Small and with tendency to trophic change	Annular lesions, if present, larger
Pseudovesicles and even bullæ though rare.	No vesicles.
Palmar lesions small, translucent, sand-grain papules, no scale.	Palmar papules larger round, shotty flat and deep, with collarette of peripheral scales.

in many cases, and the lesions less suggestive. On the other hand, the resemblance between the horny papules of "lues cornée" and those of folliclis may be very striking, and differentiation on purely objective grounds very difficult (see Fig. 541).

Lesions of papulonecrotic tuberculid may occasionally be abundant enough about the extremities to suggest papular syphilid at first glance but the scars of crops of lesions usually assist in recognition, and the typical necrotic-centered lesion is, of course essential.



Fig. 303.—The papulonecrotic tuberculid of the face, usually confused with syphilis. See Fig. 304 for differential characteristics and Fig. 301 for another excellent example showing recovery under arsphenamine treatment. Note the necrotic-centered papules on the ear.

Fig 304

"ACNITIS"	PAPULAR LUES II
Essential lesion papule with dried necrotic central plug.	Essential lesion papule without central hard necrotic plugging (may be scaling, however)
Typical lesions often found on the lobe and concha of the ear	Ears not usually involved and no typical lesions.
Pitted, varioliform scars of former lesions or crops usually common.	No scars (unless excoriated or pustular).
Mucosa and genitalia not involved.	Mucosa and genitalia commonly involved.

Fig 305.

PAPULONECROTIC TUBERCULIDS OF THE FINGERS (FOLLICLIS)	PAPULAR LUES II
Typical tuberculid papule with dried necrotic central plug.	Flat or scaling papule, no necrosis.
Not indurated.	Indurated.
Tendency to appear on finger-tips and backs of hands.	Tendency to appear in palm and flexures of phalanges.
Deep vesicle t onset.	No vesicle.
Painful at onset (thorn in flesh sensation)	No pain.
White or depressed punctate scars.	No scars.

Chronic Urticaria and Papular Lues II.—T the dermatologist this seems at first thought an unlikely source of confusion, yet we have seen several striking examples. The annular papular syphilid seems especially to suggest urticaria to the inexperienced. The differential elements in the

Fig 506

CHRONIC URTICARIA	PAPULAR LUES II
Seldom appears on face.	Common on face.
May be accompanied by swelling of eyelids or lips, etc.	No edema of lids or lips.
Typical fresh wheals may be found with the papules, or even bullæ or vesicles in severe cases.	No wheals or vesicles.
Wheal pits with pressure (finger-nail)	Does not pit on finger-nail pressure. Deep induration instead.
Usually gyrate and annular groups and sometimes larger wheals.	Apt to adhere to one type of lesion at least in early cases.
Lesions evanescent, changing from hour to hour and day to day	Fixed eruption, not much change except gradual evolution.
Rose-bloom pink of urticaria.	More indolent and brownish in color
No scale	May be some scaling (psoriasiform)
Very itchy	Not itchy
No mucosal lesions unless edema.	Mucosal lesions common.
No genital lesions	Genital lesions common.



Fig 507.—An eruption of "raw-ham and copper-colored spots, which is not syphilid. This is the acquired form of urticaria pigmentosa in the adult. For differential diagnosis see Fig 508. On slapping or pinching, the spots become wheals.

Fig 508.

URTICARIA PIGMENTOSA	PAPULAR LUES II
Chronic and fixed. No evolution.	Evidence of evolution of crop of lesions.
No induration.	Marked induration.
No scale.	Older lesion and psoriasiform types present scale.
Gives wheal on slapping or pinching the individual lesion, or the pigmented macule or papule	No change on slapping or pinching except increased redness.
No palmar or plantar lesions.	Palmar and plantar lesions common.
No genital lesions.	Genital erosion common.
No mucosal lesions.	Mucous erosions and papules common.



Fig. 309.—A profuse eruption of papular sarcoid lesions in woman with syphilis. Confused with papular secondary syphilid. Diagnosis previously by biopsy



Fig. 310.—A papular syphilid of the face closely resembling nodular leprosy (Courtesy of Drs. Fordyce and Wise.)



Fig. 311.—Nodular lepra of the face. The lesion as accompanied by papular syphilid hich disappeared under treatment, leaving the leprous lesions unaffected. Note the leprous ulcer of the tongue. (Courtesy of Drs. Fordyce and Wise.)

eruption as such, apart from concomitant evidence of the presence or absence of syphilis, are given in Fig. 306.

A variety of urticaria known as urticaria pigmentosa, especially in the adult, because of its production of copper-colored spots, seems to be confused ith papular syphilids. The differential table (Fig. 306) applies t the adult (Fig. 307) and infantile (Fig. 706) types.

Nodular Lepra and Papular Lues II.—The papular lesions of nodular or mixed type of lepra may assist in the frequent confusion of this disease with syphilis. This must be especially



Fig. 312.—Papular eruption of leprosy simulating secondary syphilid (Collection of Drs Fordyce and Wise.)



Fig. 313.—Mycosis fungoides resembling leprosy and the papular infiltrative syphilid. (Courtesy of Drs. Fordyce and Wise.)

borne in mind because of the possibility of biological false positives with the Wassermann reaction in this disease (see Chapter IV) The leprous papular eruption especially when confined largely to the face, just before the development of the diffuse infiltration or leonine facies, may when

accompanied by alopecia due to infiltration of the eyebrows and scalp, create picture which at first glance defies the expert. In considering this differentiation Fig. 488 should be consulted in

Fig. 314.

NODULAR LEPRA	PAPULAR LUES II
Nodules larger coarser deeper less sharply defined.	Papules smaller more superficial and distinct, though indurated.
Infiltrated plaques or diffuse thickening common.	Confluence unusual No diffuse infiltration.
Very slow evolution—months or years.	Comparatively rapid evolution—weeks.
Nerve changes (mixed type)	No nerve changes.
Buccal lesions rare.	Buccal lesions common.
Cicatricial ulcerative changes.	No cicatricial ulcerative changes.
Positive nasal smear (Hansen)	No lepra bacilli in nasal smear
Lepra bacilli in tissue or lymph.	*Spirochete pallida*, but no lepra bacilli.
N palmar lesions.	Palmar lesions common.
No genital lesions.	Genital lesions common.

addition to the following. The neurological changes if present assist materially in the differentiation (Figs. 310–312, 314)

Annular Papular Syphilids

Dermatophytosis and Annular Lues II.—"Ringworm seems to be common pitfall in the diagnosis of late annular syphilids, but it may also be very important factor in early syphilids, in which the comparative sparseness of the lesions and their predilection for the face tend to deceive the inexperienced. The annular syphilid is papule, and as such has the raised border and indurated feel of ring-shaped infiltration. The differential elements are given in Fig. 315

This differentiation does not, of course, include the pustular or agminate follicular trichophytoses and the kerionis or macaroon-like trichophytic granuloma, which are not likely to be

Fig 315

DERMATOPHYTOSIS	ANNULAR LUES II
Lesions apt to be solitary or geographic group.	May be solitary but more apt to be several and scattered.
Superficial, no induration.	Definite deep cord-like induration, though perhaps not marked.
Peripheral satellites, evidence of auto-inoculation or extension about large lesion.	Satellites unusual (unless in corymbose configurations)
Vesicles and pustules (may be minute) recognizable in border with hand lens.	N vesicles or pustules.
Quit actively inflammatory as rule	Usually indolent, dull color.
Ringworm fungus detectable by microscopic examination of scales treated with KOH solution (20 per cent.)	N ringworm fungus in scales.
More inclined to scale.	More likely to be indurated, smooth, non-scaling.

confused with the annular syphilids. It does not include, furthermore, the trichophytoses of the scalp, which produce patchy alopecia in childhood, and in the case of the scarring ringworm, favus, permanent cicatricial alopecia. The tendency of the arsphenamines in certain patients to cause the flare-up or extension of dermatophytic lesions, with the appearance of ringed erup-

Fig. 316.

ANNULAR SEBORRHEIC DERMATITIS	ANNULAR LUES II
Localizes in seborrheic area face, presternal, interscapular regions.	Except for the face, no special localization.
Superficial, no induration.	Deep induration.
Surface may show minute vesicles.	No vesicles.
Distinct tendency to follicular involvement (puncta)	Surface tends to be smooth, shiny slightly scaling, and translucent.
Scales yellowish, oily	Scales (if no concomitant seborrhea) dry grayish.
No genital lesions.	Common on genitalia, especially scrotum.
No mouth lesions.	May be concomitant mouth lesions.

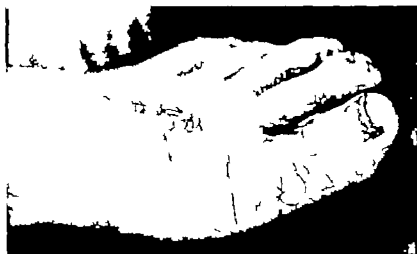


Fig. 317 —A moist secondary syphilid (eroded papule) resembling dermatophytosis between the toes. (Patient of Dr Herman Beerman.) This is the type of case reported by Thomas and Bluefarb (1940) as an occasional source of diagnostic error



Fig. 318.—Annular secondary syphilid of the face. Note the dryness, the scale the indolence all of which distinguish it from impetigo (Fig. 319) For differential diagnosis from ringworm see Fig. 316.



Fig. 319.—A characteristic impetigo contagiosa of the face. For differential diagnosis see Fig. 322.



Fig. 320.—Annular syphilid of the arms. (Collection of Dr. F. G. Harris.)



Fig. 321.—An annular papular type of recurrent syphilid. This woman's original secondary eruption was apparently macular and was called measles. This eruption was diagnosed "chronic hives." For differential diagnosis see Figs. 306, 308.

Fig. 322.

IMPETIGO CONTAGIOSA	ANNULAR LUES II
Face and fingers favorite sites.	Face, extremities, trunk.
Superficial, no induration.	Definite induration.
Moist, crusted, with areola. Often bullous margin. Ca be rubbed off, leaving an oozing surface	Dry no crust, occasionally slight scale In the skin, not on it.
Actively inflammatory bright red, yellowish or reddish crusts.	Very indolent. F wn pink t brownish red.
Rapidly progressive, day to day	Little change in week or more.
In hairy regions especially superficial pustules may be present.	No pustulation.
Polycyclic border geographic contours on extension.	Usually individual ares and rings.
Itches and burns.	No symptoms.

Fig. 323.

PITYRIASIS ROSEA (Annular Type)	ANNULAR LUES II
Usually abundant, but not always.	Rarely profuse (except in negroes)
Often confluent over hips.	Lesions usually discrete.
Rare on face.	More common on the face.
Typical lesion an oval patch with pink superficial slightly raised scaling border, cigarette-paper crinkled center	Typical lesion a ring with firm palpable indurated border yellowish to brownish dull pink color Slight scale, center simply slightly scaling or normal.
Axial arrangement in cleavage lines.	No axial arrangement, though occasionally a suggestion of it in lesions below the scapula.
Premonitory primitive lesion often found.	N premonitory lesion.
Pseudovesicles may occur	N vesicles.
No mouth lesions.	May have mouth lesions.
No genital lesions.	Common on the penis and scrotum especially

Fig. 324

ANNULAR LICHEN PLANUS	ANNULAR LUES II
Rare on the face.	Common on the face.
Rings small (0 5 t 2 cm)	Rings larger (2 to 7 cm.)
Typical papules, flat, angular superficial and shiny may be found. Rings often composed of such lesions.	If ring is composed of papules, the individual units are larger rounded, deeper indurated.
Color violaceous with brownish tinge	Color paler yellowish to brownish pink.
May be marked trophy t sites of involuting lesions.	Little or no trophy
Lichen planus lesions in the mouth (silvery retiform net ork)	Annular papular or mucous erosive lesions in the mouth.
Lichen planus lesions on genitalia (see Figs. 393, 420)	Syphilitic lesions on genitalia (see Figs 416, 417 418)

those in the flexures and on the body must be borne in mind as an element of confusion with syphilitic annular eruptions and cutaneous relapses. Bismuth is also described as responsible for an annular pityriasis rosea-like eruption (Chapter VI)

Annular Seborrheic Dermatitis and Annular Lues II.—This eruption may at times cause some annoyance as a source of error especially in persons with marked and obvious seborrhea

or oily skin (Fig. 490). In general, annular syphilids are more conspicuous and obviously out of the ordinary than are the annular lesions of seborrheic dermatitis. The variety of seborrheic der-



Fig. 285.—Characteristic atrophic remains of annular lesions in lichen planus on the thigh For details of this case see Fig. 287

Fig. 286.

ERYTHEMA MULTIFORME (Iris Type)	ANNULAR LUES II
Localization to the extremities, especially the backs of the hands.	Localizes on face and trunk. Rare on hands.
Mucous membranes severely involved. Extensive bullous lesions and erosions. Lips livid.	Mucous lesions apt to be few and indolent.
Marked fetor	No fetor
Elementary lesion, wheal-like ring with central bulla.	Ring only. May be double, however. Central normal skin or slight scale.
Dark red or bluish-red color in concentric rings.	Indolent pinkish-yellow or brownish-red color
Large lesions may be urticarial or bullous and become denuded and exudative.	No bullae or scale.
Desquamates on involution if severe, but acute lesion rarely scales.	Slight scaling on fully developed lesion.

Fig. 287

GRANULOMA ANNULARE	ANNULAR LUES II
Rare lesion, usually solitary	Not a common syphilid.
Usually occurs on hands, face, neck, and may appear on trunk and extremities.	Unusual on the hands.
Usually non-inflammatory	More inflammatory
Deep papular arciform infiltrates in cutis.	Usually more superficial, though infiltrated and firm.
Chronic and of long duration.	Runs a more rapid course.
No other evidence of syphilis.	Concomitant evidence of syphilis
Distinctive histologic picture.	Histology that of syphilis.

matitis described as seborrhea petaloides, while an unusual one, may be quite deceptive on purely objective grounds

Impetigo Contagiosa and Annular Lues II.—This is the common superficial streptococcic or staphylococcic infection of the skin characterized by an eczematous oozing seropurulent exudat



Fig. 328.—The grouped follicular secondary syphilid. A magnification of these lesions is shown in Fig. 329.



Fig. 329.—Enlargement of the macular-follicular lesions in Fig. 328. Note the papular accentuation of the follicle mouths, the grouping, and the combination of erythema and hyperpigmentation in the groups.

from   circular patch of deep red inflammatory reaction with the formation of crusts. Peripheral extension in rings from an involuting center is frequent. It may be differentiated from an annular syphilid by the considerations shown in Fig. [illegible].

Pityriasis Rosea, Annular Types, and Annular Lues II.—Compare this differentiation under macular and papular types of eruption. The identification of typical elementary lesions and axial arrangement are important features (Figs. 290, 292, 325)

Annular Lichen Planus and Annular Lues II.—*Lichen planus rarely produces profuse annular type of eruption.* On the other hand, groups of such lesions may occur about the wrists and on the back and thighs, which may be quite confusing. The annular lichen planus of the penis



Fig. 381.—A profuse follicular syphilid, showing disappearance of the grouping on the arms.

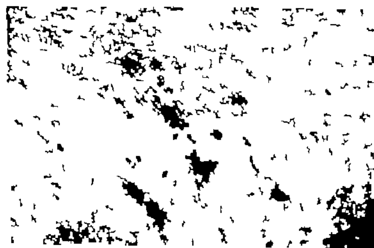


Fig. 380.—Magnification of a corymbose arrangement of papular-follicular secondary syphilid.

and scrotum, unless accompanied by mouth and other lesions, may puzzle the most expert (Figs. 299, 324, 325, 393, 410).

Erythema Multiforme (Iris Type) and Annular Lues II.—While erythema multiforme is, as a rule, a very acute affair, the chronic indolent types at times associated with a tuberculous diathesis, and the acute forms with mouth lesions, furnish the basis for some very serious errors in diagnosis. The response of erythema multiforme to arsphenamine increases the possibility of error (Figs. 366, 376–379).

Granuloma Annulare and Annular Papular Lues II.—The lesions of granuloma annulare, usually solitary and few in number are more apt to be confused with those of late syphilis than early We have, however seen multiple lesions in which the differential diagnosis required some study (Fig 572)

Chronic Urticaria and Annular Syphilids.—This differentiation is covered in Fig 306.

Fig. 332.

PERIFOLLICULAR SEBORRHEIC DERMATITIS	FOLLICULAR LUES II
Localized in seborrheic areas, sternum, and interscapular region. Rarely seen elsewhere.	Occurs in flank, ver abdomen and arms as well back.
Lesions not distinctly grouped. Large ir regular patches common.	Distinct small groups.
Definite dermatitis, with tendency to confluence of follicular lesions. Scaling and redness.	N dermatitis in the groups. Simply pigment. No confluence.
Follicles patulous and conspicuous, no real papule at follicle mouth.	Definite papule t follicle mouth.
Margin of patches pink, center yellowish pink.	No marginal differentiation of lesion.
A greasy yellowish plug may be present in the follicle mouth.	A definite papule with or without plug.
Thin yellowish oily scale.	Little or no scale.
Miliary vesicles or pustules may be found.	No vesicles or pustules unless in mixed follicular and pustular types.



Fig 333.—The perifollicular type of seborrheic dermatitis. Eruption confined largely to the back Note the confluent macular lesions on the upper flank.

FOLLICULAR SYPHILIDS

Perifollicular Seborrheic Dermatitis and Follicular Lues II.—Seborrheic dermatitis, among its polymorphous possibilities, embraces a type which may bear definite resemblance to follicular syphilid on hasty inspection. This is especially true of the macular follicular syphilid. Seborrheic dermatitis usually loses its initial follicular character early in its course, however and



Fig. 334.—The lichenoid dermatophytid simulating the grouped follicular secondary syphilid. The patient had an extensive ringworm of one leg.

assumes the confluent patchy dermatitic characteristics which render its differentiation from syphilids comparatively easy (Fig. 333).

The Lichenoid Dermatophytid and Follicular Lues II.—These lesions may at times be almost indistinguishable except by concomitant evidence of syphilis and therapeutic response. The dermatophytid, however is always secondary to a focus of ringworm infection, as the follicular tuberculid, called lichen scrofulosorum, is to a focus of tuberculosis. If a dermatophytic focus or lesion can be demonstrated, the presumption is in favor of a dermatophytid. The difficulties of

diagnosis are apparent from Fig. 334. The papules of the dermatophytids are more apt to be spinous than are those of the follicular syphilid, in which the essential lesion is more a perifollicular fleshy papule than a spinous plug. The groups of the dermatophytid tend to be larger and fewer in number. These are at best, however, only uncertain distinctions, and the entire case must at times rest on the demonstration of concomitant syphilis and the absence of ringworm focus.

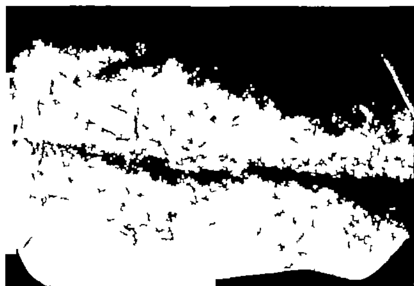


Fig. 336.—An extensive lichen scrofulosorum, simulating grouped follicular secondary syphilis.



Fig. 335.—Lichen scrofulosorum, accompanying tuberculous hydrarthrosis of the knees. For differential diagnosis see Fig. 337.

Lichen Scrofulosorum (Tuberculid) and Follicular Lues II.—This is at times an important differentiation, though a relatively rare one. The follicular tuberculid may like the dermatophytid be an accompaniment of a tuberculous focus, such as a joint involvement or a glandular lesion, and assist in the differentiation of the primary condition from syphilis (see Fig. 609). The principal points in the differentiation of the cutaneous lesion are given in Fig. 337.

Pityriasis Rubra Pilaris and Follicular Lues II.—While Devergie's disease is a comparative rarity, it at times presents a puzzling picture. The elementary lesion is a follicular papule which

as the disease progresses extends toward confluence with neighboring lesions, producing a diffuse dermatitis over considerable areas or the entire body. The lesions are first found on the neck and forearms, and the spinous plugging of the follicles on the dorsums of the fingers is quite characteristic (Fig. 338). Very extensive and acute follicular syphilids may, however, at times produce this picture.

Fig. 337

LICHEN SCROFULOSORUM	FOLLICULAR LUES II
Large nutmeg-grater or goose-flesh patches are more common than the smaller follicular groups in adults.	Small, closely set, widely disseminated groups of lesions.
Most abundant on abdomen and flank. No other types of generalized cutaneous lesion present.	Most abundant over back and extremities, and most typical on the back. Macular and papular lesions often present.
No alopecia.	Alopecia a common accompaniment.
Elementary lesion a yellow, almost flesh-colored papule.	Elementary lesion a pink or dull red papule. More active looking eruption.
Groups less pigmented than those of the *follicular syphilid.*	Groups more pigmented.
No genital lesions.	Genital or mucosal lesions may be present.
Concomitant signs of tuberculosis may be present.	Concomitant evidence *of* *casual* syphilis may be present.



Fig. 338.—Note the "plugging" of the follicles on the dorsums of the phalanges. This is characteristic of pityriasis rubra pilaris, not the follicular syphilid. See Fig. 339.

Keratosis Pilaris, Lichen Spinulosus, and Follicular Lues II.—Keratosis pilaris is a relatively common affection, essentially a follicular type of ichthyosis. It may vary in severity from a slight accentuation of the follicles on the extensor surfaces of the upper arms to a diffuse and extensive follicular nutmeg grater plugging of the follicles in the flanks and over considerable areas, especially on the extensor surfaces (Fig. 340).

Follicular Lichen Planus and Follicular Lues II.—This is a rare lichen planus lesion, but one which we have seen confused with syphilid. The eruption consists of scanty small groups of pap-

Fig. 339

PITYRIASIS RUBRA PILARIS	FOLLICULAR LUES II
Universal distribution, including face, neck, body and extremities.	Face free.
Large patches.	Small groups of 5 to 15 papules.
Coarse nutmeg-grater ppearance nd feel.	Comparatively fine
Spinous follicular horny plug conspicuous feature.	Papule at follicle mouth, seldom spinous plug.
Tendency t confluence of patches.	Patches remain discrete.
Dermatitis with scaling develops confluent patches and becomes general.	No dermatitis, no scaling.
Follicular plugging, backs of fingers.	Fingers rarely involved.
Very slow and chronic course.	Comparatively rapid course.

ules, 2 to 5 in the verage lesion, small and noninflammatory Associated lesions of lichen planus of other types are usually present and are essential for diagnosis (Fig. 340) The follicular lesions

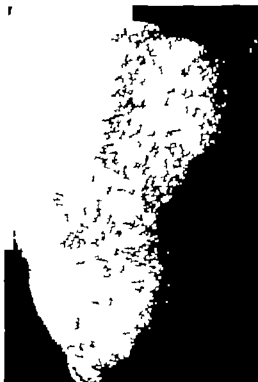


Fig 340.—Follicular lesions of the keratotic type over the right scapular region. These might represent keratosis pilaris, lichen spinulosus or follicular lichen planus (hich is the correct diagnosis). For differential tables see Figs. 341 342

of lues II are coarser more inflammatory the groups larger and better defined. Other signs of syphilis can usually be found in harmony with the stage of the disease

Fig. 341

KERATOSIS PILARIS	FOLLICULAR LUES II
Most pronounced on extensor surfaces and where follicles are normally prominent and abundant.	Most pronounced on back. Definitely recognizable even in softer parts of skin.
No grouping. May be some scattered large patches.	Definite small groups, rarely any confluence.
No hyperpigmentation.	Hyperpigmentation in the groups.
No alopecia.	Alopecia common accompaniment.
A spinous plug rather than follicular papule the essential lesion. Long duration, often since childhood.	A papule, not plug
One type of lesion, except for occasional miliary pustules.	Papular and macular secondary lesions may be coincident.
Often signs of concomitant ichthyosis (ichthyosis follicularis). Look for parchment palms and scaling forehead and shins.	Concomitant evidence of active syphilis.

Fig. 342.

LICHEN SPINULOSUS	FOLLICULAR LUES II
Slender spine projecting from the follicle mouth, the essential lesion.	No spine, or only slight horny plugging.
No papule or only slight elevation.	Papule definite.
Non-inflammatory	Mildly but definitely inflammatory
Grouping less conspicuous.	Grouping characteristic.
No pigmentation.	Hyperpigmentation of the groups.
No alopecia.	Alopecia common scalp lesion. Other lesions of active secondary syphilis.

Fig. 343.

ALOPECIA AREATA	SYPHILITIC ALOPECIA
Large patches few in number	Small patches, numerous, with some diffuse thinning.
Geographic outlines common (perfect circles, arcs)	Widely and evenly disseminated, giving moth-eaten appearance to sides of scalp.
Patches often completely bald.	Patches often not completely denuded
Sharp margin of almost normal hair density	Margins often fade into thinned hair

Fig. 344.

ALOPECIA OF CHRONIC ERYTHEMATOUS LUPUS	SYPHILITIC ALOPECIA
Few and scattered irregular patches of partial or total baldness.	Many small patches, usually smaller than those of lupus erythematosus.
Characteristic atrophy often with almost scarlike changes and telangiectasia.	No permanent atrophy or scarlike changes.
Permanent hair loss.	Usually temporary hair loss.
Signs of concomitant erythematous lupus.	Signs of concomitant early syphilis.
May show follicular plugs at borders.	No follicular plugs.



Fig. 345.—The typical moth-eaten alopecia of secondary syphilis. The process is often better seen at the sides and back of the head, where the hair is more closely clipped. A doubtful case is often made easily apparent by a close hair cut.





Fig. 346.—Typical alopecia areata. The patches are bald without scarring, and may contain sparse white hairs. The same process may involve the beard. This type of alopecia and alopecia totalis is sometimes seen in heredosyphilis, but there is no necessary connection.



Fig. 347.—A moth-eaten alopecia associated with acute disseminate erythematous lupus. Recovery. The alopecia of the scalp produced by the discoid (chronic) type of this disease is permanent, and leaves an atrophic scar due to destruction of the hair follicles.



Fig. 348.—Alopecia is much more difficult of identification in the woman than in the man, on account of the longer hair but it may be detected above the forehead, ears, and nape of the neck, and, as in this case, in the eyebrows.

Every clinician should learn to watch eyebrows. The clue to secondary syphilis, lepra, leukemia, may be found there. It is curious fact that picture of this kind, shown to an audience of men physicians is rarely identified; but when shown to an audience of women (nurses), the alopecia of the eyebrows is singled out at once.

It is justifiable to take blood Wassermann test on every patient who complains of the loss of any considerable amount of hair within short time.

This patient had no other signs of secondary syphilis except positive blood Wassermann reaction. She was first seen with large satellite bubo in the cervical region, huge tonsils, but no evidence of a primary lesion. The differential blood count, which showed successively 67.4, 79 and 63.5 per cent small mononuclears before treatment, led to suspicion of lymphatic leukemia. The count fell quickly to 43 per cent and the nodes subsided when treatment for syphilis was begun. Lymphatic leukemia rarely produces alopecia.

Syphilitic Alopecia

When it is borne in mind that the typical alopecia of syphilis has many of the characteristics of the follicular syphilid of the body minus the papular lesion and the hyperpigmentation, the alopecias, such as that of alopecia areata and of the trichophytoses, may be discarded almost at a glance. The alopecia produced by erythematous lupus of severe and extensive type, of which disseminate erythematous lupus is the best example, may be patchy and moth-eaten (Fig. 347) We have seen the permanent alopecia produced by discoid erythematous lupus that had been



A



B

Fig 349 —The alopecia of lepra (B) may be almost indistinguishable from that of secondary syphilis (A) Both patients had lost the outer thirds of the eyebrows. For differential diagnosis of syphilis and lepra see Fig 497

unusually abundant on the scalp deceive dermatological group until typical lesions appeared on other parts of the skin.

The alopecia of favus, the scar-producing ringworm infection, is coarsely patchy with distinct depressed scarring and permanent removal of hair in the affected areas. Active scutula of sulphur yellow color and mousy odor may be found around the old lesions. The alopecia of the juvenile ringworms is usually partial and involves the top of the head, with large oval or circular patches in which the hairs are in part gone, in part broken off or stunted and friable. Cicatricial alopecia also produces large patches comparatively few in number or solitary with an essential lesion of follicular pustular type and atrophic scarring



Fig 330 —A factitial alopecia produced by pulling the hair with the fingers. Neurotic patients can occasionally produce puzzling alopecias.

PUSTULAR SYPHILIDS

Variola (Pustular) and Pustular Lues II.—The essentials of this differentiation are considered under papular lues II. The course of variola is more likely to have revealed its true identity by

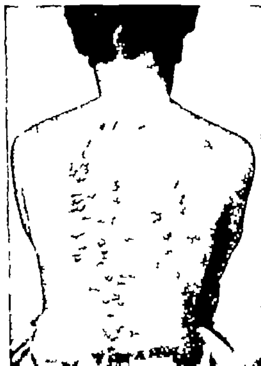


Fig. 331 —Small pustular syphilid in colored woman, of type apt to be confused with small-pox. For differential diagnosis see Fig 294 (Collection of D J F Schamberg.)

the time it has reached the pustular than when it is in the papular stage The variola pustule is prominent, elevated, highly inflammatory and on the trunk often presents an areola, while the syphilitic pustule is, on the other hand, flatter softer more indolent, crusts early and is less abundant, as rule than the variola lesion. Umbilication is quite distinctive of the variola pustule as compared with its practical absence in secondary syphilids. Variola lesions on the mucous membranes are easily distinguished. I cases occurring during epidemics of variola it is better



Fig 352 —An eruption of smallpox, mistaken for syphilis and admitted t venereal ward. For differential diagnosis see Fig. 294 (Collection of Dr J F Schamberg.)



Fig. 353 —A severe form of rupia in an unusually malignant syphilis. The lesions are of eighteen months duration and ere but l ttle affected by course of neoarsphenamine Recovery followed the use of arsphenamine ("606") and mercury rubs simultaneously For another illustration of rupia see Fig 89

Fig. 334.

ACNE CACHECTICORUM	PUSTULAR LUES II
Typical sequence of seborrhea, comedones, sebaceous retention cysts, deep inflammatory nodules, pustules and abscess formation, with scarring	No necessary association with comedones, sebaceous cysts, etc.
Limited to acne area of the body (face, back, chest)	Scattered over body
None in scalp.	Not uncommon in scalp.
Lesions markedly inflammatory often painful and furuncular	Lesions indolent, crusted papule, more in the skin itself less deep subcutaneous reaction.
Much pus, little crust.	Little pus, much crust
Scarring usually prominent in comparison with number of lesions.	Lesions prominent in comparison with small number of scars.

Fig. 335.

PYODERMA	PUSTULAR AND RUPIAL LUES II
Often associated with acne cachecticorum or follows variola.	No necessary association with acne
Scalp not often involved (except nape of neck).	Scalp often involved.
No definite configuration.	Grouped and gyrate configurations may be present.
Process mainly subcutaneous with under running soggy edges.	A cutaneous ulcer punched out.
Canalization with pus sinuses, multiple abscesses, etc.	No canalization, sinuses, or subcutaneous burrows.
Skin blue, soggy hemorrhagic, over considerable areas.	Skin only affected at site of lesion.
Little or no ulceration, and when present superficial and ecthymatous.	Ulcers rupial, deep, punched out, and granulating.
No crusts.	Crusting conspicuous.



Fig. 336.—Pyoderma and ecthyma following variola, and mistaken for syphilis. The canalization of the face with pus sinuses rarely occurs in syphilis. Compare Fig. 501 (late syphilid of the face)

to isolate the doubtful patient, especially if unvaccinated, though not with active cases of variola, pending decision, which should not rest wholly upon blood Wassermann report (Figs. 351 352).

Acne Cachecticorum and Pustular Lues II.—Acne cachecticorum is the severe acne of the back, based upon the typical comedone-papule-pustule-cyst sequence of acne vulgaris, but ex

Fig 357

ECTHYMA	PUSTULAR AND RUPIAL LUES II
Rarely involves scalp or face.	Common on scalp and face.
Superficial ulceration, border irregular shelving or undermined, fissured.	Rupial ulcer usually deep, punched out, granulating, round or oval.
Crusts flat, not so thick, suggest impetigo.	Crusts lamellated, thick, "oyster-shell, "turtle backed, or dished.
Follicular pustules, impetiginous patches, superficial blebs or flaccid pustules and sometimes furuncles, suggest pyogenic origin.	Lesions scattered, surrounding skin little affected, inflammatory areola and other signs of infection few
Background of ecthyma low resistance, diabetes, nephritis.	Background of syphilis; but Wassermann reaction may be negative.

aggerated often to huge proportions in persons who are markedly debilitated or who are the victims of some special though unknown predisposition. The lesions may or may not involve the face and chest (Figs. 354, 358)

Pyoderma and Pustular or Rupial Lues II.—The canalization of the infected skin by pus sinuses suggestive of scrofuloderma or even an actinomycotic infection may likewise in some



Fig. 358.—Scarring and active lesions of acne cachecticorum. (See Fig. 354)

cases suggest to the inexperienced, syphilid. This is particularly true of such lesions on the body Occasionally such nonspecific imitations of syphilids may prove highly puzzling as in Fig 356.

Ecthyma and Pustular Lues II.—Ecthyma is ulcerative form of pyogenic infection, essentially an ulcerative impetigo. It occurs in children, debilitated patients who are rendered susceptible by diabetes and nephritis, and those who are the victims of old age and bad hygiene.

Acne Scrofulosorum (Papulonecrotic Tuberculid of the Body) and Pustular Lues II.—The tuberculids of the body do not usually occur alone, but are apt to be accompanied by the more distinctive and easily recognized folliclis of the hands, the facial lesions of acnitis, or the leg lesions of erythema induratum. The differential diagnosis is sometimes extremely important, for patients with tuberculid may present partial positive blood Wassermann reaction with highly cholesterinized antigens, and the rapid response of the lesions to arsphenamine as we have seen, may suggest a syphilid. All adenopathies in which syphilis may be a factor regardless of their apparently tuberculous character should be searched for the scars of tuberculid. The acute extensive tuberculids of the body which may be confused with early syphilids usually occur in childhood, and are essentially miliary tuberculosis of the skin with grave prognosis (Fig. 359).

Acne Necrotica (Acne Varioliformis) and Pustular Lues II.—Acne necrotica is a papular eruption with the distribution of pustular seborrheic lesions and the morphology of papulonecrotic tuberculid. It usually involves the face, especially the forehead, the hair line, the presternal and the interscapular regions, but may occur in the scalp, and, in fact, in that situation may cause much confusion if the scarring be abundant. The scar is varioliform and were it not for its distribution would be very difficult to distinguish from that of a tuberculid or small pustular

Fig. 360

ACNE SCROFULOSORUM	PUSTULAR LUES II
Usually sparse and prone to localize on the extremities.	No pronounced tendency to localize on the extremities.
Chronic course, successive crops of lesions, seasonal incidence (spring and fall) large proportion of scars, few lesions.	More rapid course, more lesions, fewer scars, no seasonal history
Scars varioliform, scattered, no grouping or configuration.	Occasionally definite grouping and annular configurations.
Elementary lesion must be identified to make diagnosis [illegible] papule with definite necrotic center, dried central brown plug that can be picked out, leaving depression. Short vesicular no pustular stage.	Elementary lesion [illegible] pustule or papulopustule with crust and exudate, but not the typical necrotic central plug.
Removal of necrotic plug leaves conical pit.	Removal of crust leaves moist purulent ulcer
Other characteristic tuberculids such as erythema induratum.	Other lesions of syphilis.
Systemic tuberculosis, especially glandular	Systemic signs of syphilis.

syphilid. Groupings and configurations may be seen which are at times very confusing. The disease affects debilitated young or middle-aged women and men, and is of unknown etiology (possibly streptococcal). It does not respond distinctively to treatment for syphilis (Fig. 360)

DIFFERENTIAL DIAGNOSIS OF EARLY SYPHILIS OF THE MUCOSAE AND MUCOCUTANEOUS JUNCTIONS

The objective morphological differentiation of syphilis of the mucous surfaces is often more difficult than that of the skin, and resort to laboratory evidence, especially the darkfield, is much less confidently made. The mouth and the genitalia are, as has been seen, the habitat of spirochetes distinguished with difficulty from *Spirochaeta pallida*. Conditions such as moisture and secondary infection often reduce lesions to a nondescript uniformity in a short time, and make it imperative therefore that lesions of the mucous membranes be seen as early in their course as possible if their important characteristics,





Fig. 260.—Acne varioliformis (acne necrotica) showing the typical distribution to the face, especially the hair line and scalp margin, and to the back. The eruption may be more extensive. Note the necrotic-centered papules. The lesions are not crusted. For differential diagnosis see Fig. 263.

and still more their evolution are to be correctly interpreted. The mucous membranes may furnish during considerable periods of the disease and especially in relapsing cases, the only objective suspicion arousers and at the

same time the most dangerous lesions of the disease from the standpoint of transmission. The most painstaking habit of examining the mucosae and the anogenital region therefore is essential to the successful detection of a most



Fig. 361.—Severe papulonecrotic tuberculid of the face (acnitis), resembling pustular syphilid. This patient had been receiving mercury and iodide for supposed secondary syphilis, without effect.



Fig. 362.—Effect of seven arsphenamine injections (0.3 to 0.4 Gm.) on the tuberculid (acnitis) shown in Fig. 361.

Fig. 363.

ACNE NECROTICA (Acne varioliformis)	PUSTULAR LUES II
Confined to face, hair line, scalp, and presternal and interscapular regions except in rare severe cases.	Occurs on trunk as well and without marked predilection for sebhorrheic areas.
Typical lesion suggests tuberculid, not a syphilid—a necrotic-centered papule—but there may be some acneiform lesions.	No distinctive necrotic center to any lesions.
Lesions few and scattered at any one time.	More distinctly crop-like outbreak.
Scars white, varioliform, always present and abundant in comparison with number of active lesions.	Scars few or none in proportion to active lesions. Smaller lesions leave little scar.
Process very chronic.	Process more acute.
While below par, patients seldom show much constitutional effect.	Constitutional effects likely to be pronounced. Concomitant evidence of early syphilis.

important part of syphilis. The steps in the technic of examination of these regions, as given in Chapter II, should be strictly adhered to, and the possibility of syphilis be constantly kept in mind.

Some authors apply the term "acne agminata" to lesions of this type and do not regard them as tuberculids.

an indurated tonsil can sometimes be aspirated with a tonsil anesthetizing needle and lesions of the tongue and lip with a hypodermic needle Markedly



Fig. 308.—This lesion passed as hemorrhoid ith several physicians. When told to make darkfield examination one of our staff prepared for spurt of blood by putting a ligature in position around it before beginning t scrape. The lesion teemed with *Spirochaeta pallida*. Note the infiltration of the median raphe of the scrotum, the first point t suggest that the lesion was condyloma rather than hemorrhoid Ulcerating or eroded hemorrhoids with few symptoms should be regarded with suspicion.



Fig. 309.—Squamous cell epithelioma t the anus. Notice the sharply defined pearly border of the flat lesions. The process xtended 1½ inches into the anus. Such lesions may arise from leukoplakia. There no gross evidence of syphilis n thi case

enlarged lymph nodes associated with tonsillar lesions or lesions on the lip and tongue may be aspirated in accordance with the technic described in

Chapter III before a decision is made as to their character but smaller isolated nodes should not be disturbed if there is suspicion of carcinoma.

Streptococcal Angina and Syphilitic Angina.—Sore throat is one of the commonest accompaniments of the generalization of syphilitic infection, and frequently passes for a banal infection

Fig. 370.

CARCINOMA OF THE TONSIL	SYPHILIS OF THE TONSIL
Unilateral.	Lues I unilateral, Lues II bilateral
Tendency to crateriform destructive ulceration.	Infiltration and erosion rather than destruction.
A raised pearly or nodular border may be recognizable.	Border seldom raised or distinctive.
Much necrosis, confined to lesion.	Exudate but not much necrosis.
Stony hardness.	Elastic, but firm induration (Lues I)
Infiltration of pillars.	Pillars edematous rather than infiltrated.
May find Vincent flora.	May find *Spirocheta pallida*.
Lymph-nodes apt to be small or moderate in size in proportion to lesion.	Lymph-nodes apt to be large, even huge, in proportion to lesion.
Glands appear late	Glands appear early
No signs of secondary lesions on skin.	Secondaries may be present elsewhere
Get blood Wassermann test.	Get blood Wassermann test.
Specimen from the lesion shows carcinoma.	Specimen from the lesion shows chronic inflammation, but may suggest lymphoma or even lymphosarcoma and tuberculosis (no tubercles, however)

during an indefinite period until some conspicuous sign calls attention to its syphilitic origin. The taking of blood Wassermann tests more frequently if not routinely on sore throats, especially if they show evidence of chronicity and the habit of stripping patients for examination, even for so small a matter as a sore throat, would lead to the detection of a good deal of secondary syphilis in its incipiency The severe syphilitic angina and the streptococcal throat have the following differentiating points (Fig 371)

Fig. 371

STREPTOCOCCAL ANGINA	SYPHILITIC ANGINA
Acute onset, rapid course.	Slow onset, slow course.
Tonsillar at the outset, but may have only strawberry pharynx.	General angina, patches on pillars.
Membrane thick, furry yellowish or greenish.	Exudate grayish, thin, pellicle-like.
Much edema, especially palate and uvula.	Little edema Unilateral infiltrate in chancre and may be more edema.
Very angry red.	Redness only moderate.
Patient acutely ill, high fever fast pulse.	Patient loses weight but seldom high fever or fast pulse.
No cranial nerve palsies.	Third, seventh, and eighth nerve involvement may occur but rare.
No neuroretinitis or iritis.	Neuroretinitis and iritis to be looked for
Patient may be more ill than appearance of throat justifies.	Patient usually less ill than appearance of throat justifies
No mucous lesions in mouth.	Mucous lesions at commissures and lips, tongue, and pillars.
No papules on tongue.	May have papules on dorsum of tongue
No alopecia.	Look at hair and eyebrows.
May have acute toxic erythema, palms diffuse red or free.	May have roseola or papular syphilid, look for palmar papules.
No general adenopathy	General adenopathy including epitrochlears.
If not over in ten days, take repeated blood Wassermann tests.	Take more Wassermann tests "on suspicion.

Diphtheria and Syphilitic Angina.—This confusion is much too frequent cause of diagnostic error. If the habit of taking a blood serologic test on seeing "throat" could be made as common as that of taking culture, some tragic cases of extragenital and early genital infection, especially in women, could be earlier diagnosed. Suggestive objective differential points are as follows (Fig. 272)

Fig. 272.

DIPHTHERIA	SYPHILITIC ANGINA
Acute onset, rapid evolution.	Gradual onset, slow course.
White, grayish, or blackish necrotic membrane, embedded in the surface involved.	Pale gray exudat pellicle or pearly pseudomembrane over surface.
May slough, especially on tonsil.	Not likely to slough.
Bleeds on removal of pseudomembrane.	Oozes serum on removal of pellicle.
Edema, but not infiltration.	Brawny infiltration in Lues I.
Usually bilateral	Lues I unilateral.
Adenitis present, often tender acute, early and local.	Adenitis present, indolent, discrete, unilateral, not tender General in Lues II
Culture, Klebs-Löffler	Culture, negative, streptococcus, sometimes Vincent flora.
Toxic symptoms of diphtheria heart, peripheral neuritis, glossopharyngeal especially	Second, third, seventh, and eighth nerve involvement suspicious, but rare. Heart rarely shows disturbance clinically
N cutaneous lesions (except rare diphtheritic lesions)	Cutaneous signs of syphilis.
Headache not conspicuous.	Headache important symptom.
Antitoxin if in doubt, but take blood Wassermann test too.	Repeated blood Wassermann tests positive.
N lesions of syphilis elsewhere on mucosa.	Look for mucous patches under lips and in commissures, and papules on the tongue.

Fig. 273.

DIPHTHERIA. PAPULAR SYPHILID OVERLOOKED

Female, age fifty-nine, married, housewife.

Ambulance case arrived vomiting excruciating headache, paralysis of left side of face. Throat, membranous pharyngitis and tonsillitis.
No fever pulse nd heart normal.
Seen by medical man, who called laryngologist.
Seen by otolaryngologist, who took culture. House officer took Wassermann. Catheterized urine taken.
Neurologist called, reported probable luetic facial palsy Recommended lumbar puncture
Smears reported negative
SWR ### (second day)
Blood-pressure 170/90

Dermatologist called fourth day to see eruption on wrist. Found patient literally covered with maculopapular secondary syphilid, of seventeen days standing which had not been noted in any previous examination.
Liver and spleen enlarged.
History of vaginal discharge.
Husband, ge sixty-three examined ten days later found t have maculopapular Lues II and involuting primary lesion.
The home physician had given him some pills.
Wife's Spinal Fluid (end of first course)
W R. negative 4 c.c. Nonne positive
24 lymphocytes.

Discussion

1 The home physician was culpable in his management of the husband' case Mercury does not control infectiousness Mercury by mouth ha no place whatever in early syphilis except as an djunct.

2. Never too old for lues.

3 Never look at a bad throat without looking at the skin. A glance t the skin in this case ould have saved four days of special examinations.

4 Syphilitic pharyngitis and tonsillitis can present severe involvement diphtheria or Vincent angina.

Vincent's Angina and Syphilitic Angina.—Too much reliance on smears with ordinary stains, and failure to think of syphilis among the first possibilities in throat are the general causes of confusion here. Arsenicals should be voided in therapeutic tests because of the occasional effect on Vincent infections (Fig. 274).

Agranulocytic Angina and Syphilitic Angina.—The agranulocytic reaction to the arsenicals and bismuth as well as the idiopathic type and that with aplastic anemia from other causes, may be momentarily confused with severe syphilitic lesions of mouth and throat. The severe mouth and throat reactions to antisyphilitic drugs are described on page 403. Fig. 375 summarizes the differential points.

Erythema Multiforme and Syphilitic Angina.—Erythema multiforme of the iris type is an acute eruptive process usually incident upon bacterial invasion of the blood stream. The lesions

Fig. 374.

VINCENT'S ANGINA	SYPHILITIC ANGINA
Rapid, acute, destructive process.	Slower more indolent, less destructive.
Exudate yellow abundant.	Exudate pearly scant.
Marked necrosis.	Little necrosis, or none.
More inclined to involve soft palate and uvula.	Less inclined to involve soft palate and uvula.
Dorsum of tongue and commissures and lips free.	Look for mucous lesions and papules in these sites.
No cutaneous lesions.	Cutaneous lesions of syphilis may be present, but not necessarily. Look at palms and soles, axms, genitalia.
Don't trust darkfield to eliminate syphilis.	Aspirate the lesion if possible.
Adenopathy local.	Adenopathy likely to be both local and general.
Use the Wassermann test routinely	

on the skin range from purpuric macules through heals, usually annular and often with bullous centers (iris lesions—Fig. 378), to the deep subcutaneous tender infiltrations of nodose erythema. While hemorrhagic and petechial macular and papular syphilids have been described (Kalz 1940) they are extremely rare. Lesions on the mucous membranes of the mouth are common associates of the cutaneous picture, and in some instances may occur alone in repeated attacks before the final appearance of lesions on the body which identify the process. We have seen this disease so many times confused with syphilis, and even treated for it, that we have always laid much stress

Fig. 375.

AGRANULOCYTIC ANGINA	SYPHILITIC ANGINA
Evidences of mild or more commonly severe infection.	Rarely much constitutional reaction.
Ulcerations in pharynx or on tonsils.	Scant exudate—no ulceration.
May show deep gangrenous destruction.	Little or no necrosis.
Adenopathy usually absent.	Adenopathy present.
No exanthem (unless purpuria)	Usually concomitant cutaneous lesions.
Marked leukopenia.	Usually normal white count.
Rarity of granulocytes in differential count.	Differential blood count normal or slight lymphocytosis.
Frequently fatal termination.	Gradual involution of process—rapid with treatment.

on its differential diagnosis and have come to regard it as an unrecognized source of error for many physicians. In fact, the first case of erythema multiforme in our experience, whose diagnosis was confirmed by several subsequent years of observation, was, when first seen in 1912, in process of being demonstrated to a class of students as a syphilid clearing up under arsphenamine. The response of erythema multiforme to arsphenamine is often quite striking and accounts for the possibility of error from therapeutic tests begun with this drug.

The essential differential lesion of erythema multiforme is bulla, and once its characteristics

are firmly fixed in mind, and the practical exclusion of syphilis in the adult by the finding of bullae in the eruption is accepted, it becomes easy to differentiat erythema multiforme in the



Fig. 376.—A ruptured bulla of erythema multiforme on the lip. The condition is often taken for syphilis at first sight, especially if the lesions are for the time being limited to the mouth. It responds therapeutically t the administration of neoarsphenamine. In suspected cases examine the backs of the hands (see Fig. 378) For differential diagnosis see Fig. 380.

mouth from syphilis, provided complet examination of the patient is made (Fig. 380) Special attention should alw ys be paid to the backs of the hands, on which the characteristic iris lesions



Fig. 377.—The mouth lesions of erythema multiforme are bullae When they rupture they leave an eroded surface ith ragged remnants of pellicle A show the top of ruptured bulla on the under side of the upper lip B show an erosion simulating a mucous patch at the angle of the mouth, a sit of predilection for mucous patches. For differential diagnosis see Fig 380.

are most apt t appear (Fig 378) For differential points involving the lesions on the mucous membranes see Fig 380. Lesions upon the genitals are rare but they do occur

Malignant Pemphigus and Early Syphilis of the Mucous Membrane.—The type of pemphigus which is associated with the early appearance of bullous lesions on the mucous membranes, subsequent appearance of bullae on the skin, and ultimately fatal outcome has seemed to be more common during the past several years, and the possibility of its confusion with syphilis,



Fig. 578.—Several types of lesions of erythema multiforme on the hands to assist in identifying lesions on the mucous membranes. The cutaneous lesions vary from pink macules to hemorrhagic bullae and are not invariably present. Those shown are the iris type.

therefore, deserves consideration. Malignant pemphigus is of unknown cause. It may attack persons of any age from youth to senility. The prodromal period of mouth lesions unaccompanied by any lesions on the skin may last for several years, with an increasing degree of severity until finally bullae begin to appear about the genitalia and then upon the skin, with comparatively

rapid and fatal progress of the disease with extensive denudation and infection of the entire skin, condylomatous hypertrophy of the bases of the ruptured bullae in the flexures and apposed or



Fig 579 —Erythema multiforme resembling an extensive circinate syphilid.

Fig 580.

MUCOUS LESIONS OF ERYTHEMA MULTIFORME	MUCOUS LESIONS OF EARLY SYPHILIS
Mouth more involved than throat.	Throat apt to be more in olved than mouth.
Process acut	Process more chronic.
Essential lesion ruptured bulla.	Essentiul lesion an eroded papule.
Pellicle tough, mucous membrane-like, shreddy yellowish	Pellicle thin, grayish or pearly easily iped off.
Confluence of lesions common.	Lesions tend to be discrete.
N papules on dorsum of tongue.	Look for papules on dorsum of tongue
Lips and mucosæ livid.	Lips nd mucosæ normal color
Mouth very sore	Mouth not very sore.
Marked fetor may be extreme	*Little or no fetor*
Genital lesions rare	Genit l lesions common.
Previous severe ttacks usual	Previous severe ttack not usual
Bullous lesions, wheals, iri lesions elsewhere (may not be present) Look t backs of hands.	Indolent lesion of syphilis (no bullæ in halt) usually present. Look for palmar papules

ternal surfaces. The differential points in lesions of the mucosae and genitalia are shown in Fig 584.

Aphthae (Mouth and Genital) and Early Syphilis of the Mucous M embranes.—The aphthous lesion may be, but is not necessarily manifestation of herpes, and is often an accompaniment of infections, evidence of hich can usually be found on examination. Aphthous ulcers may

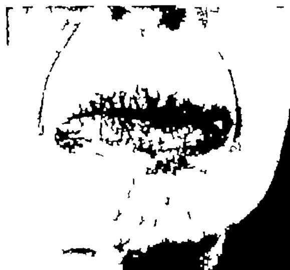


Fig. 381.—A severe grade of mucous erosion usually taken for trench mouth, or in its early stages suspected of being syphilitic, but, in reality due to pemphigus of the malignant type (see Fig. 384).

be accompaniments of intestinal allergies. The characteristic morphological earmarks of herpes the tense, itching, burning, deep vesicles, often grouped, must be borne in mind. In the mouth



Fig. 382.—Condylomas and mucous erosions produced by malignant (vegetative) pemphigus. These lesions and those in the mouth may appear before the bullae on the skin.

the lesions are usually single and the early rupture leads to the formation of small ulcer which is usually very painful. The differential points are shown in Fig. 384 (see also Fig. 387).

Periadenitis Mucosa Necrotica Recurrens and Mucosal Syphilis.—This relatively uncommon condition responds promptly to arsenicals and thus may give the impression of syph-



Fig 583 —Circinat and arciform bullous lesions of pemphigus. For practical purposes ther is no bullous syphilid in dults.

Fig 584.

MALIGNANT PEMPHIGUS	MUCOUS LESIONS OF SYPHILIS
Essential lesion flaccid bulla. (Repeated observation of mouth and throat ma be needed to find one before rupture) Rupture of the lesion lea es an erosion hich heals ith difficulty	Essential lesion papule or erosion. Never bullous in dults.
Look for bullæ in larynx, especially if hoarseness is present.	No bullæ Simply edema and t times slight ulceration.
Pellicle fragile but may sometimes be found just after rupture er erosion	Pearly exudat rather than shred of membrane
Confluent geographic areas, especially over soft palat and uvula.	Little tendency t confluence.
Lesions often appear first about the gums.	Lesion rare on gums.
Mouth very sore	Soreness not extreme
Fetor pronounced	Fetor usually slight.
Surface of tongue usually free until lat	Papules early on tongue surface
Bullæ lat on skin.	N bullæ but other syphilitic lesion
If condylomas present identify bullæ and superficial erosions.	If condylomas present, look for papular or maculopapular syphilid.
Darkfield negative for *Spirochæta pallida*.	*Spirochæta pallida* may be found (caution)

lid, as in 2 out of 3 cases seen by one of us (J H. S.) The larger lesions in the dorsum of the tongue may give the impression of gumma of the tongue but the lesions in the lip or side of the tongue are more suggestive of indolent aphthae. The first case in this experience responded

a therapeutic test for syphilis and was regarded as such for several years, until a second case was encountered in which the nonsyphilitic character of the lesion was undoubted. The first case responded with rapid healing to 3 injections of arsphenamine on several occasions,

Fig. 385

APHTHAE (MOUTH)	LUES II MUCOUS MEMBRANE
Elementary lesion deep vesicle which ruptures and ulcerates.	Elementary lesion papule which erodes.
Ulcer yellow necrotic, excavated.	Erosion flat or slightly depressed, with pearly pellicle.
Ulcer usually 1 to 3 mm. in diameter	Erosion 5 to 10 mm. in diameter
Marked inflammatory areola.	Little reaction about lesion usually
Painful.	Little or no pain.
If any grouping, usually herpetic.	If any grouping, usually arciform.

APHTHAE (GENITAL)	LUES II GENITAL
Definite ulcer depressed border (vesicular stage rarely seen)	Eroded papule.
Angular irregular or stellate.	Margin usually rounded
Necrotic or yellowish base.	Flat or elevated, faint pearly pellicle.
No condylomatous hypertrophy	Condylomas common.
Painful.	Relatively painless.
Darkfield, no *Spirochaeta pallida*.	Darkfield, abundant *Spirochaeta pallida*.

although the involution without the drug was very slow The condition is of unknown etiology The elementary lesion is a nodule beneath the mucosa which enlarges, becomes tender and finally separates a sequestrum following which the lesion heals (Fig. 391)



Fig. 386 —Erosions resembling mucous syphilids, developing on penis and scrotum in a patient susceptible to phenolphthalein.

Marginal and Exfoliative Glossitis (Benign Plaques) and Mucosal Syphilis.—Fortunately even a limited experience enables the beginner to distinguish the more marked examples of marginal glossitis from syphilids of the tongue. The solitary benign plaque, however occurring on the dorsum, is sometimes mistaken for syphilitic leukoplakia or for a mucous patch, from which



Fig. 387 — Aphthous" ulcer on the labium, associated with arthritis and mouth lesions. A similar type of lesion may develop in the condition known as ulcus acutum vulvae. A portion of the labium had been excised for a previous attack. Aphthous lesions may also rarely occur on the scrotum and be confused with mucous erosions. For differential diagnosis see Fig. 388.

Fig. 388.

PERIADENITIS MUCOSA	LUES II MUCOUS MEMBRANES
Elementary lesion deep hard nodule.	Elementary lesion flatter, more superficial papule.
As usually seen, deep ragged excavation, *sometimes with yellow slough.*	Usually level or a shallow flat depression, *with a grayish pellicle.*
Active inflammatory areola.	N inflammatory areola.
Lesions seldom more than one or two at time.	Lesions may be numerous.
Very painful.	Relatively painless.
Darkfield, no *Spirochaeta pallida.*	Darkfield, *Spirochaeta pallida* may be present.

Fig. 389

MARGINAL AND EXFOLIATIVE GLOSSITIS	LUES II MUCOUS MEMBRANES
Confined t tongue margin and dorsum.	Lesions t commissures and on lips, palate, faucial pillars, and tonsils as well.
Plaques if present tend t be anterior t middle of tongue.	Plaques tend to be posterior near circumvallate papillae
Annular or gyrate lively reddish patches with grayish margins, and flat gray plaques on dorsum.	Red papules on dorsum, gray erosion on margin.
Geographic and concentric contours.	N geographic contours.
Dry no erosion or exudate.	Erosion and exudate on marginal lesions especiall
No induration.	Indurated papules on dorsum.
	Concomitant signs of syphilis

later it is really distinguished if it is found that what appears to be gray pellicle is, in reality not removable.

Lichen Planus (Buccal) and Mucous Lesions of Syphilis.—Lichen planus continues its imitation of the eruptive manifestations of syphilis on to the mucous surfaces, and pads the unofficial lists of "leukoplakia" by the inclusion of lesions for which the term is essentially a misnomer. The differentiation is shown in Fig. 390.

Fig. 390.

LICHEN PLANUS (BUCCAL)	LUES II (BUCCAL)
Stellate and punctate mosaic network.	Scattered or isolated, rounded plaques or papules.
Lesions minute (0.5 to 2 mm.).	Lesions larger (4 to 10 mm.).
Silvery color	Flesh color (except leukoplakia).
No erosion. Lesion can be wiped dry without change.	Erosion the rule. Wiping the lesion removes exudate.
Lesions rare on fauces and gums.	Lesions common on fauces, occasional on gums.
No symptoms whatever	Some soreness from erosions.
Lichen planus lesions elsewhere usually present.	Syphilids elsewhere on body

Tuberculous and Syphilitic Fissures and Erosions.—Tuberculosis of the mucosae and syphilis may be distinguished with great difficulty at times on morphological grounds. Therapeutic tests should be made with a soluble mercurial salt to avoid nonspecific temporary arsphenamine effects. The presence of miliary tubercles in the inflammatory periphery of a tuberculous lesion



Fig. 391.—Severe "aphthous" type of ulcer on the tongue. This condition is periadenitis mucosa necrotica recurrens" (see Fig. 388), which may also respond to arsphenamine treatment.

if discoverable is a helpful point. At times the diagnosis can with difficulty be made even after complete study including tissue sections (see Figs. 384, 537, 535)

Heavy Metal Stomatitis and Early Mucosal Syphilis.—This differentiation is obviously of importance, and may lead to the gross mismanagement of patients under treatment, either in the form of overmercurialization under the impression that the syphilis is resistant, or of undertreatment in the supposition that the patient is hypersusceptible. Under careful mouth prophylaxis the incidence of stomatitis is so much reduced as to do away with most of the possibility of error



Fig. 392.—A condyloma of lichen planus on the foreskin. Hypertrophic lichen planus is rare on the genitalia. The usual type is the flat papule on the glans.



Fig. 393.—Another form of lichen planus of the penis. This patient had an active gonorrhea. The sheen is due to reflection of light from the surface of the papules. They have no scale.



Fig. 394.—The penile wart. The term may cover any lesion from true verruca vulgaris, as in this case, to condyloma and chancre. All such lesions should be subjected to darkfield examination. These are small papillomas, discret and hard of surface without pellicle or exudate. Their probable source is from the true warts on the hand by autoinoculation.

and careful mouth prophylaxis incidentally contributes t the control of infectious lesions through cleanliness (Fig. 396).

Ulcus Acutum Vulvæ and Lues II of the Female Genitalia.—This disease, due to the *Bacillus crassus*, affects young virgins especially and is an acutely painful form of ulceration and erosion of the mucous surfaces of the vulva, described in the literature by Lipschutz, Olson, McDonagh,

Fig. 395.

TUBERCULOUS FISSURE AND EROSION	SYPHILITIC FISSURE AND EROSIONS
Erosion or fissure usually redder more inflammatory	Erosion or fissure indolent, even non-inflammatory
Satellite glistening minute miliary papules (tubercles) around border of erosion or ulcer if lesion is on flat mucosal surface	No miliary satellites.
Tends to be painful.	Not so painful
No other definitely syphilitic mucosal lesions.	Associated papules on tongue or mucous patches
Tubercle bacilli in smear	*Spirochete pallida* in darkfield.
Tubercle bacilli in sputum	Sputum repeatedly negative
Signs of tuberculosis in chest or larynx (may be syphilis).	Signs of syphilis elsewhere on body or in larynx.
Tubercles and bacilli in tissue (don't trust mere presence of giant-cells)	Chronic inflammatory and granulomatous picture without tubercles.
Mercurial therapeutic test negative	Mercurial therapeutic test positive (soluble salt)

and Flemerud. The lesions in general conform to the description of aphthae (see differential diagnosis, Fig. 388) Vincent's angina of the vulva must also be borne in mind.

Herpes Progenitalis and Genital Lues II.—It has been held that patients with syphilis are especially prone to relapsing herpes of the genital region, so that this differentiation is occasionally

Fig. 396.

MERCURIAL STOMATITIS	LUES II, BUCCAL
Edema of tongue with dental incisures in margin.	Little local edema, especially of tongue.
Erosion and ulceration, especially of apposed surfaces and crypts.	
Exudate grayish-yellow abundant.	Exudate pearly scant.
Color livid	Color paler red.
Much necrosis and detritus.	Little necrosis or detritus.
Fetor marked.	Fetor slight or none.
Edema, lividity and bleeding of gums, with separation from teeth.	May be patches on gums, but gum tissue firm, pale, not hemorrhagic, not separating from teeth.
No papular lesions (unless those of syphilis)	Papular lesions often found (tongue, dorsum)
Soreness on clenching teeth.	No soreness on clenching teeth.
Marked local adenopathy	Adenopathy general; no local.

BISMUTH STOMATITIS	LUES II, BUCCAL
Marked fetor	No fetor
Black line in gum margin.	No black line.
Pigment patches on mucosa.	No pigmentation.
Other signs as with mercurial stomatitis.	Other signs as with syphilis.

important but seldom difficult, especially if seen early. It should be borne in mind that true herpetic lesions in early syphilis may be infectious and transmit syphilis (Fig. 397).

Lichen Planus and Genital Lues II.—Lichen planus may furnish imitations of syphilids upon the genitalia, especially of the annular type, which, while not strictly mucous lesions, are more deceptive than those in the mouth. It is essential for the practitioner in making differentiation

to learn the appearance of the angular flat, shiny papule of lichen planus (see Fig. 298) The annular lesion of lues II may present shiny surface.

Scabies and Genital Lues II.—The localization of scabies to the genitalia usually occurs in *males, and lesions of both scabies and syphilis may be present It is important to realize, first,* that scabetic burrow or papule may be chancre if sexual intercourse has occurred since the development of the scabetic lesion. One of us (J H. S.) has seen 6 scabetic burrows on the shaft

Fig 297

HERPES PROGENITALIS	LUES II, GENITAL
Essential lesion vesicle	Essential lesion a papule.
Grouped closely usually one or tw groups.	Not grouped, and may be widely scattered or arciform.
Confluent with polycyclic border	Discrete.
Inflammatory areola.	Indolent, not markedly inflammatory
Inclined to crust if exposed.	Dry if exposed.
Yellow necrotic base if ulceration and infection occur	Grayish exudative pellicle if moist.
Characteristic itching or burning prodrome.	N symptoms, or slight soreness after lesion develops.

of the penis, from five of which *Spirochaeta pallida* was obtained on scraping, the infection being traced to intercourse with chambermaid just before her secondary eruption appeared and she came under treatment. The sign manual of the individual scabetic lesion is, of course, the burrow which on the genitalia forms a wavy or irregular elongated papular elevation as contrasted with the round papule of syphilitic lesion. It must be remembered that papulo-erosive syphilids may

Fig. 298.

LICHEN PLANUS GENITAL	LUES II GENITAL
Elementary lesion quadrangular or polygonal papule.	Elementary lesion an oval or round papule.
Papule is small (0.5 t 2 mm.)	Papule is larger (2 to 10 mm.)
Annular lesions are segmented into miliary papules.	Annular lesions usually continuous ring
No erosion occurs even on moist surfaces.	Mucous erosion frequent.
Lesions may be flesh colored, but are often whitish or gray	Lesions usually flesh colored.
N induration	Fleshy induration not uncommon.
Other lesions of lichen planus in skin and mouth	Other lesions of syphilis

develop upon scabetic papules in the patient who has both diseases. The identification of the scabetic infection by the localization of typical lesions to finger webs, forearms, axillae, nipples (women) waist line, and anogenital region, ith nocturnal itching prominent symptom, is essential.

THE CONSTITUTIONAL ASPECTS OF EARLY SYSTEMIC SYPHILIS

Symptoms of Generalization.—The generalization of a syphilitic infection is accompanied in a certain proportion of cases by systemic symptoms and constitutional manifestations which may range from slight malaise to the gravest prostration and cachexia. In general, the symptoms are surprisingly mild, considering the extent of systemic involvement shown by pathologic and experimental study They may begin as early as a week after the appearance of the chancre. The proportion of cases in which there arise constitutional symptoms sufficiently marked to attract the patient s attention certainly does not exceed 50 per cent (47 1 per cent in our series) Fournier estimated that

50 per cent of women and 75 per cent of men experience no significant constitutional symptoms from their infection.

Our own experience accords with his. Sixty-three per cent of women and 48 per cent of men in our series had constitutional symptoms from their infection. No reason can be assigned for the preponderance of women. It is notable that they as a sex are in similar proportion more reactive to intensive (five-day etc.) treatment for syphilis. The general health in either sex may remain unaffected at times even in conjunction with the most malignant eruptive phenomena and severe grades of internal change, and patients have even told us they had not known what good health was until they developed an early syphilid.

The constitutional symptomatology of early syphilis does not in general have a high diagnostic value. Here and there a distinctive symptom stands out, but in general corroborative evidence must be sought from a thorough general examination and the serologic tests before a diagnosis can be made. An account of the symptomatology of early syphilis will, however, assist in arousing suspicion and lead to fuller investigations of special cases in which constitutional symptoms may be the only expression of the infection, or in which confusion with other diseases is possible.

Fig 300

SYMPTOMATOLOGY OF EARLY CONSTITUTIONAL SYPHILIS

	Per cent.		Per cent.
Sore throat	53	Iritis	3
Malaise	42	Vaginal discharge	3
Headache	24	Anemia	2
Loss of weight	18	Deafness	2
Fever	14	Hoarseness	2
Meningismus	8	Myositis and myalgia.	2
Gastro-intestinal symptoms	7	Nocturnal ostealgia	2
Rheumatism	7	Periostitis	1
"Neurotic" symptoms	5	Arthritis	1
Bone complaints	5	N VII palsy	1
Pseudotuberculous symptoms	5	Insomnia (essential)	1
Nervousness	4		

The conspicuous place occupied by the *syphilitic angina* is at once apparent, and the importance of more than a local examination of patients who complain of sore throat may be inferred. The stripped examination and routine serologic test (Thomas and Goldstein 1941) would save many blunders (see Figs. 348 373). *Headache*, if persistent, is an important symptom of secondary syphilis. If the occipital head pain of meningismus be included in this group, the proportion rises to 31 per cent. Nearly a third of all syphilitics who have any constitutional symptoms whatever to bring them to a physician, therefore, complain of headache. The combination of persistent headache and sore throat in any practice would yield a harvest of early syphilis if adequately investigated or given a routine serologic test and an inspection of the skin. On the other hand the anginal symptoms of infectious mononucleosis must be kept in mind, and heterophile antibody test and differential blood count invoked. Sadusk (1941) found 7 per cent of infectious mononucleosis presenting a macular eruption. Absence of hand and foot lesions and large cervical adenopathy speak against syphilis. *Fever* of a mild grade, seldom exceeding 100° F afternoon temperature is a fairly common accompaniment of the constitutional manifestations. Several types are described with great minute-

ness by Fournier but those for which the general clinician should be most on the alert are the irregular slight afternoon rise suggesting tuberculosis or endocarditis and the intermittent fever associated with a "typhoid" state of prostration and cachexia with a sparse roseola. This "syphilitic typhoid," while rare, is at times exceedingly puzzling.

Pseudotuberculous Symptoms.—The combinations of slight fever loss of weight, night-sweats, gastro-intestinal symptoms, asthenia, nervous irritability and cough which early syphilis may present are important from the standpoint of differential diagnosis for tuberculosis. The impossibility of diagnosing syphilitic pneumonitis by any intrinsic sign makes it difficult to decide just how often errors actually arise from the confusion of these two diseases in their early stages. Cough is an unusual symptom in early syphilis, but pseudotuberculous pictures made up from the other elements in the table are so far from unusual as to justify a serologic test on all cases of suspected early tuberculosis. Again the biologic false positive in atypical upper respiratory infections (virus pneumonia?) must be recalled. Arthritic pains with anemia and loss of weight, another group of symptoms by no means rare in both diseases, demands careful scrutiny The combination is one of the chief causes of error in the misdiagnosis of tuberculids as syphilis. The well-recognized possibility that a syphilitic infection superimposed on a latent tuberculosis may cause a flare-up of the latter must always be borne in mind.

Headache and Head Pain.—Fournier with characteristic detail distinguishes three types of head pain which can be identified in early syphilis. The commonest is a *diffuse cephalalgia*, possibly the expression of a low-grade encephalitis but of unknown etiologic mechanism Second, in our experience is *meningismus or occipital headache* with occasional stiffness of the neck, associated with cases of basilar meningitis. The least common type is the localized area of osteitis giving rise to *spotlike pains* in the head exactly localizable by pressure on the affected areas. The tendency to a nocturnal character of syphilitic headache, while recognized, is often exaggerated in diagnosis, and should not lead to neglect of proper investigation of persistent headache of any type.

Gastro-intestinal Symptoms.—In early syphilis these may range from anorexia to the nausea and projectile vomiting associated with intracranial pressure in high grades of early cerebral and meningeal involvements. Nausea, vertigo and vomiting, with deafness and tinnitus, is an expression of changes in the eighth nerve, the vertigo nausea and vomiting expressing the vestibular part of the complex. The symptoms of the not uncommon syphilitic catarrhal gastritis of the early stage are not highly specific, although Eusterman has called attention to the frequency of subacidity (see Chapter XVII) Reynolds (1942) has described an interstitial inflammation in secondary syphilis with stenosing possibilities. Fournier describes syphilitic bulimia and a pseudo-hysterical anorexia.

"Rheumatism"—The catch basket of "rheumatism" expressing the osseous arthritic and myalgic symptoms of early syphilis, is responsible for frequent errors in diagnosis. The systematic use of a reasonably sensitive serologic test under proper control in all aspects of bone, joint, and muscle involvement in patients between the ages of fifteen and thirty would, without question reap a considerable harvest of early syphilis. Many of these "rheumatic" symptoms have the vagueness expressed in the lay term "grippy" That they may constitute the prodromes or early manifestations of the gen

eralization of the infection makes their recognition especially important. Traditionally the leading symptomatic feature of the bone changes of early and recurrent syphilis is pain nocturnal in character exaggerated by heat and relieved by movement of the affected part. Overemphasis of these peculiarities would lead to the overlooking of a number of cases since in not more than half the patients with osseous changes under our observation has this syndrome appeared. Wile and Senear (1916) found 56 per cent of their early cases to present actual clinical bone lesions.

Osseous System.—The bone lesions of syphilis are fully described in Chapter XVI, and the following résumé simply completes the symptomatic picture of secondary syphilis.

Periostitis.—This involves especially the long bones, the tibia being, by all means, the most frequent. Early syphilitic periostitis, clinically is sharply localized process, seldom covering more than few square centimeters and presenting as somewhat doughy elevation of the bone, noninflammatory without any sign of fluctuation. On the tibia the lesions develop most often on the anterior face and edge. Its most distinctive feature is the highly localized point of exquisite tenderness which can be found by searching the entire surface of the tumefaction with the finger tip. The tenderness on pressure at this one point, in contrast to the insensitiveness of the remainder of the lesion, may be so exquisite as to result in shriek of protest from the patient. Slighter

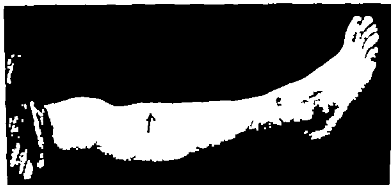


Fig. 400.—A typical localization for syphilitic secondary periostitis. The roentgen-ray examination is negative.

degrees of periosteal involvement in bones covered by muscles, when not marked enough to produce tumefaction, may be detected by gripping or wringing the extremity as described in the technic of examination. Periosteal changes over the sternum, the clavicles and scapulae, and the ribs are seldom observed, probably because not looked for. Periosteal changes may lead to actual productive growth of bone, forming definite thickenings and exostoses which can be detected clinically.

Ostealgia is the term applied to the indefinitely localized bone pains of secondary syphilis for which no pathologic background can be found. A fair proportion of the diffuse headache of the secondary period, and sternalgia and pleurodynia, as Fournier points out, belong under this category and are especially common in women.

Osteomyelitis.—Wile and Welton (1941) report this in early syphilis, and Plan and Frazier (1941) report 2 cases following blood transfusion (same donor). Reynolds and Wasserman (1948) review the literature of destructive lesions and believe them not uncommon. Pathologic fracture also occurs.

Arthritides.—These are relatively uncommon in secondary syphilis (only 1 per cent in our series). Part of this rarity is due to lack of complete investigation, especially in women. Low or insignificant grades of inflammatory reaction, an unusual retention of mobility, pain without any evidence of actual lesion, and exaggeration on rest and relief by movement are the conspicuous points. Hydrarthrosis is not common, according to Fournier. True polyarthritis in early syphilis is known to occur but is very rare and, t judge by reported cases, presents little that is really characteristic.

Tenosynovitis, Bursitis.—These features of early syphilitic involvement of the skeletal system are rare, and in our experience have presented no distinctive features from which diagnosis could be made without resort to collateral evidence.

Myopathies.—Myalgia is a common complaint among the nondescript general symptoms of early syphilis, and presents no distinctive features. It may be associated with varying degrees of muscular weakness, or with actual amyotrophic changes, on the authority of Fournier although this complication must be very rare. One of the bizarre and rare myopathies of secondary syphilis is contracture of the biceps. There is no visible or palpable pathologic change beyond the fixation of the arm in a semiflexed position. Myositis in secondary syphilis may be recognized by the usual signs of localized tenderness of the muscle tumefaction, pain on movement, etc.

Lymphatic System.—Involvement of the lymphatic system in secondary syphilis is one of the most characteristic aspects of this stage of the disease. Seventy per cent of cases in our experience present this feature (Tomé y Bona, 1936 85 per cent) Clinically three groups of lymph nodes in addition to the inguinal are most often concerned in the adenopathy—the suboccipital, the cervical (especially the posterior cervical) and postauricular and the epitrochlear Axillary inframammary submental, and submaxillary groups are usually unaffected. The nodes are discrete usually painless may be sufficiently enlarged to be easily visible and never break down. We have not known the uncomplicated general adenitis of syphilis to reach the proportions of the marked adenitis of early Hodgkin s disease or lymphatic leukemia in white patients, but Moore (personal communication) states this may occur in Negroes (Fig 348) The grade of lymphatic involvement has little relation to the severity of the affection, and may be marked or absent in cases exhibiting a distinctly malignant tendency General adenitis may be one of the earliest signs of the generalization of the infection, and is at times the first thing in a general scrutiny of the patient which suggests syphilis and leads to a painstaking search for confirmatory evidence. The epitrochlear enlargement, when marked and symmetric, has high suggestive value. Beeson (1935) found 27 per cent, in early syphilis

Lymphangitis in secondary syphilis is, in my experience an excessively rare complication It is indolent, cordlike, noninflammatory usually affect the long lymphatic chains such as the brachial, and may be confused on superficial examination with phlebitis. It may develop on the dorsum of the penis, as already mentioned, t the time of or just before the appearance of the secondary eruption.

Visceral Syphilis in the Secondary Period.—Syphilis of the gastro-intestinal tract and of the liver and spleen are fully discussed in a special chapter so that their existence merely requires mention here.

The Liver—Syphilitic hepatitis of varying grades of severity is an occasional feature of the florid stage of syphilis, and is more fully discussed in Chapter XVIII. I the form of *icterus gravis* it may be a precocious manifestation, assuming an alarming form before the secondary eruption is fully developed. The milder grades of involvement are associated with slight painless enlargement of the liver mild icteric tinge t the sclerae, with slight discoloration of the skin, and bile in the urine The mild type presents no distinctive peculiarities. I modern practice it is essential t distinguish it from the icterus produced by the administration of arsphenamine, and from intercurrent catarrhal and infectious jaundice (see p 873) differentiation rendered difficult at times by the fact that the therapeutic shock of the first arsphenamine injection may cause slight flare-up of a subthreshold syphilitic process in the liver

Splenic Enlargement.—Splenic enlargement as show by Wile and Elliott can be recognized by palpation in about 26 per cent of patients during the florid secondary stage This proportion drops to about 5 per cent in latent and late syphilis. As contributory evidence in the bsence of more obvious signs, this splenomegaly has value, though it fails to distinguish acute syphilis

from such infections as typhoid and malaria, which it may simulate. On the other hand, suspected early tuberculosis which presents splenic enlargement deserves painstaking search for evidence of early syphilis. The palpable spleen should always be looked for in the routine examination, and it times arouses important trains of suspicion in examining patients with bone lesions, "neurasthenia," etc.

The Kidney.—Renal irritation of the type usually associated with febrile constitutional conditions and acute infections may form part of the clinical picture of early syphilis in small proportion of cases. Small amounts of albumin, occasional casts, and red blood cells appeared in 7 of 80 cases studied by Kolmer and Klauder. These authors believe such changes to be due to actual spirochetal invasion of the kidney. There were no changes in renal function.

Acute Syphilitic Nephritis.—The distinctive nephropathy of early syphilis is the so-called acute syphilitic nephritis, distinctly rare complication, beginning frequently before the appearance of the eruption. The average onset is about the fifth month of the infection. It may, however, be delayed. A late appearance is, however, strongly against an unqualified diagnosis of acute

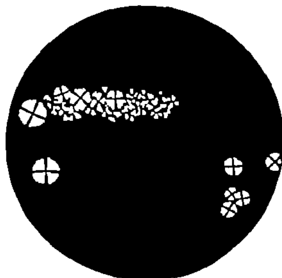


Fig. 401.—Double refracting lipoid globules, as seen by polarized light, from the urine of patient with acute syphilitic nephritis, or rather parenchymatous nephritis in the course of syphilitic infection. The upper group of globules are contained in the body of lipoid or waxy cast.

syphilitic nephritis, since chronic or subacute parenchymatous nephritis and nephroses in syphilis are not *ipso facto* of syphilitic origin and may show no response to treatment.

Abrupt onset early in the course of the infection, marked edema even to anasarca, progressive weakness with anemia, and surprisingly little effect on the general health in other ways, mark the clinical picture with minor variations. The urine exhibits characteristically tremendous albuminuria, which is almost distinctive in itself. It has repeatedly been observed to boil solid, and 83 Gm. per liter have been reported. Casts may be present in the numbers found in cases of puerperal eclampsia; epithelial débris, but little or no blood is present. Much emphasis has been placed on the presence of double-refracting lipoids in the urine (Fig. 401). Their detection requires polarizing microscope (Nicol prisms) which is seldom available. Stokes has had occasion to realize that the finding of these lipoids is only of qualified diagnostic value. *Spirochaeta pallida* has been reported in the urine by Hoffman and by Dreyer and Toepel, but under conditions which make it doubtful if the findings were authentic, or at least of renal origin. The risk of uremic complications is not considerable although Elliott and Todd have shown that an increase in blood urea occurs. Blood pressure is little affected. In differential diagnosis the clinical features of secondary syphilis may be completely masked. The Wassermann reaction has the qualified value already suggested. Absence of other causes for nephritis may arouse suspicion. The therapeutic test is without question the most important single means of identifying syphilitic nephritis. It should be performed with arsphenamine, since mercury is much less satisfactory. The latter

drug may give rise to prolongation of the renal symptoms, instead of recovery and may as in Stokes case, be powerless to prevent the onset of the complication in the first place.

The differentiation of acute syphilitic nephritis from renal irritation produced by intensive treatment with arsphenamine and mercury can be made, as rule, by the urine. The signs of renal irritation from treatment appear in the following order as the irritation progresses (1) Polyuria, (2) low specific gravity (3) casts (4) albumin (small amount) and (5) red blood cells. Those of syphilitic nephritis are in order of importance: (1) Albuminuria (marked) (2) oliguria (3) high specific gravity (4) casts (5) red blood cells. The differentiation of acute syphilitic nephritis from treatment nephrosis (high albuminuria), which incidentally seldom develops so early in the disease, is made by the absence of casts and red blood cells, and of constitutional symptoms and impaired renal function in the nephrosis. The ease of applicability and the safety of a small dosage arsphenamine therapeuti test (1 to 3 dg) which has little or no effect on the ordinary nephritis, should lead t considerable increase in the number of cases diagnosed in the future. The literature of this aspect of early syphilis is reviewed by Stokes, Cole, Elliott and Todd, Patton and Corlette.

Early Syphilis of the Eye—Neuroretinitis.—Eye complications appeared in 2.8 per cent of 3244 patients with early syphilis in the Cooperative Clinical Group series reported in 1932 Colored patients have eye involvement more than three times as frequently as white patients, and women oftener than men of both races. Involvement of the optic nerve and retina in early syphilis, while frequent, is probably not so common as some of the earlier studies made in connection with changes in the nervous system suggest. Routine examination of the fundus is necessary to detect many involvements of which the patients make no complaint, and which may rapidly disappear under treatment.

In Wile and Stokes study slight degrees of neuroretinitis were reported in 15 of 27 untreated cases routinely examined, proportion which in view of later experience is probably too high Of 62 patients with secondary syphilis who had fundus examinations, 13 per cent had definite neuroretinitis In early syphilis, the Cooperative Clinical Group found that neuroretinitis was 11 1 per cent of all eye complications. Only 2 patients in McFarland and Stokes' later series of 231 early infections, who were not the victims of neurorecurrence, presented grades of optic neuritis sufficiently marked to attract clinical attention. One of these was high-grade inflammatory process in one eye which had scarcely been noticed by the patient. In our experience involvement of the second nerve is more conspicuous and serious as manifestation of relapse in inadequately treated infections. Slight veiling of the disc should be interpreted by an experienced observer before it is reported as neuroretinitis.

Woods excellent monograph (1943) lists eye lesions in secondary syphilis in 4.5 per cent of cases and 9 8 per cent in recurrent syphilis. These include not uncommon conjunctivitis, very rare interstitial keratitis (0.3 per cent) iritis (4 per cent) the commonest lesion, plastic or nodular in type. Relapsing iritis is common with neurorecurrence. Ciliary syphiloma is now rare. Chorioretinitis is late secondary lesion probably uncommon. Chorioretinitis juxtapapillaris is an exudative lesion, and uritis papulosa stands midway between chorioretinitis and syphilitic optic neuritis. Optic nerve hyperemia often accompanies abnormal spinal fluids. Optic neuritis may be visible or retrobulbar Ch ked disc may have surprisingly little accompanying visual failure.

Disorders of the extra-ocular nerves (III, IV VI) are considered under neurosyphilitic lesions.

Iritis is usually a late secondary lesion seldom appearing before the sixth month of the infection and often as late as the second year Thirty to 40 per cent of iritis is syphilitic and iritis constitutes 73 3 per cent of the total eye complications of early syphilis. It seems to be more frequently an accompaniment of the more severe infections. The incidence in our series did not exceed 3 per cent in the general run of cases. The tardiness of the manifestation and lack of specific earmarks may lead to failure to recognize the syphilitic origin unless a routine Wassermann test is employed

According to Benedict, syphilitic iritis is plastic and passive in character cellular and serofibrinous exudate appearing between the iris and the lens ith the formation of adhesions (synechia), often total or annular in character in which latter case the iris may balloon, forming the so-called "iris bombée Pain and circumcorneal injection during the acute phase are pronounced. Papillary iritis with minute reddish papular elevations along the inner margin of the iris is quite distinctively syphilitic, and should not be confused with tuberculosis. The practitioner should always scrutinize sluggish, irregular or apparently fixed pupil in young patient with great care, and not be too ready to suspect neurosyphilis instead of old iritis with adhesions. Atropine will, of course, differentiate the two by causing dilatation of the free pupil, and demonstration of the adhesions of posterior synechia.

In severe grades of papular cutaneous secondaries, papules may appear upon the conjunctiva and at the inner canthus of the eye, and may even become pustular or ulcerate. Their accompaniments serve to identify them without difficulty J. H. S. has seen only three examples.

Interstitial keratitis and dacryocystitis may occur with the secondary outbreak, but are extremely rare complications. Interstitial keratitis and kerato-iritis occurred in 0.3 per cent of 3844 patients with early syphilis (Coop. Clin. Group) Parker (1930) gives details of 8 cases.

The Ear.—Involvement of the ear in the acute stage of syphilis includes syphilitic auditory neuritis, and acute syphilitic labyrinthitis, both of which are fortunately unusual complications, or at least rarely severe enough to attract clinical attention except in mistreated cases. They should be looked upon as manifestations of syphilis of the nervous system The Herxheimer reaction following a first injection of arsphenamine in what appears to be a patient in good condition may result in abrupt total and irremediable deafness. In these patients it is usual after the accident to obtain a history of tinnitus and beginning deafness which were present before the injection was given. Careful attention to partial deafness and the presence of tinnitus in every early infection would identify most cases and should serve as a warning to prepare the patient with mercury or bismuth and iodide before using arsphenamine. Acute syphilitic labyrinthitis is rare.

In classical example under Stokes observation, before the Wassermann test came into general use, the vomiting and uncontrollable vertigo were complete puzzle until the remains of fading roseola were identified. Auditory involvement is likely to be coincident as part of the eighth nerve involvement in the meninges and may result in ultimate deafness in spite of treatment. In Wile and Stokes series 5 of 13 cases examined for involvement of the cochlear and vestibular mechanism by reduced bone conduction and hearing tests showed evidence of changes ascribed to the disease. In view however, of subsequent studies by Goeckerman, Barlow and Stokes, we are inclined to rate this proportion also as too high for application in clinical practice The classical discussion of this field is that of Alexander in the Jadassohn Handbuch in 1929. Ciocco and Weinstein have from general study of the eighth nerve in 256 patients with syphilis, concluded that involvement of this nerve is more frequent in neurosyphilis than in other aspects of the disease but that diagnosis of syphilis cannot be based on *impaired eighth nerve function alone.*

For the practitioner the development of deafness or vestibular symptoms in young persons should be the signal for a blood serologic test and examination by an aurist.

Severe rupial lesions may involve the uricle and the canal, and papular lesions on the auricle must be distinguished from those of the papulonecrotic tuberculid of the face, which present characteristic necrotic centers. Pronounced edema of the pharynx in syphilitic angina may produce secondary symptoms of otitis media from closure of the eustachian tubes. There are no distinctive clinical earmarks of syphilitic otitis media as such, though it is said to exist.

W found that reduction of bone conduction with normal hearing, while it occurs frequently in syphilis, likewise occurs so frequently in its absence as to be untrustworthy as diagnostic criterion when taken alone.

drug may give rise t prolongation of the renal symptoms, instead of recovery and may as in Stokes s case, be powerless t prevent the onset of the complication in the first place.

The differentiation of acute syphilitic nephritis from renal irritation produced by intensive treatment with arsphenamine and mercury can be made, as rule, by the urine. The signs of renal irritation from treatment appear in the following order as the irritation progresses: (1) Polyuria (2) low specific gravity (3) casts, (4) albumin (small amount) and (5) red blood cells. Those of syphilitic nephritis are in order of importance: (1) Albuminuria (marked) (2) oliguria; (3) high specific gravity; (4) casts (5) red blood cells. The differentiation of acute syphilitic nephritis from treatment nephrosis (high albuminuria) which incidentally seldom develops so early in the disease, is made by the absence of casts and red blood cells, and of constitutional symptoms and impaired renal function in the nephrosis. The ease of applicability and the safety of small dosage arsphenamine therapeutic test (1 to 3 dg), which has little or no effect on the ordinary nephritis, should lead to considerable increase in the number of cases diagnosed in the future The literature of this aspect of early syphilis is reviewed by Stokes, Cole Elliott and Todd, Patton nd Corlette.

Early Syphilis of the Eye—Neuroretinitis.—Eye complications appeared in 2.8 per cent of 3244 patients with early syphilis in the Cooperative Clinical Group series reported in 1932. Colored patients have eye involvement more than three times as frequently as white patients, and women oftener than men of both races. Involvement of the optic nerve and retina in early syphilis, while frequent, is probably not so common as some of the earlier studies made in connection with changes in the nervous system suggest. Routine examination of the fundus is necessary to detect many involvements of which the patients make no complaint, and which may rapidly disappear under treatment.

In Wile and Stokes study slight degrees of neuroretinitis were reported in 15 of 27 untreated cases routinely examined, proportion which in view of later experience is probably too high Of 92 patients with secondary syphilis who had fundus examinations, 13 per cent had definite neuroretinitis. In early syphilis, the Cooperative Clinical Group found that neuroretinitis was 11 1 per cent of all eye complications. Only 2 patients in McFarland and Stokes later series of 231 early infections, who ere not the victims of neurorecurrence, presented grades of optic neuritis sufficiently marked to attract clinical ttention. One of these was high-grade inflammatory process in one eye which had scarcely been noticed by the patient. In our experience involvement of the second nerve is more conspicuous and serious as a manifestation of relapse in inadequately treated infections. Slight veiling of the disc should be interpreted by an experienced observer before it is reported as neuroretinitis.

Woods excellent monograph (1945) lists eye lesions in secondary syphilis in 4.5 per cent of cases and 9 3 per cent in recurrent syphilis. These include not uncommon conjunctivitis, very rare interstitial keratitis (0.5 per cent), iritis (4 per cent), the commonest lesion, plastic or nodular in type. Relapsing iritis is common with neurorecurrence. Ciliary syphiloma is now rare. Chorioretinitis is late secondary lesion probably uncommon. Chorioretinitis *juxtapapillaris* is an exudative lesion, and *neuritis papulosa* stands midway between *chorioretinitis* and *syphilitic optic neuritis*. Optic nerve hyperemia often accompanies abnormal spinal fluids. Optic neuritis may be visible or retrobulbar Choked disc may have surprisingly little accompanying visual failure.

Disorders of the extra-ocular nerves (III IV VI) are considered under neurosyphilitic lesions.

Iritis is usually a late secondary lesion seldom appearing before the sixth month of the infection and often as late as the second year Thirty to 40 per cent of iritis is syphilitic and iritis constitutes 73 5 per cent of the total eye complications of early syphilis. It seems to be more frequently an accompaniment of the more severe infections. The incidence in our series did not exceed 3 per cent in the general run of cases The tardiness of the manifestation and lack of specific earmarks may lead to failure to recognize the syphilitic origin unless a routine Wassermann test is employed

This state of affairs is natural enough. The lesions of the nervous system usually most readily detected in ordinary examination are the residua of degenerative processes, and hence of consequences rather than of antecedents, of scars rather than active lesions. Early processes, in their preventive period in the nervous system, are apt to be devoid of other than irritative signs and symptoms, and these, even, in keeping with the general rule throughout the disease, are apt to be inconspicuous. When gross signs appear they usually mean serious damage, not infrequently as in neurorecurrences involving certain of the cranial nerves, damage which is irreparable. It is essential therefore, to realize from the start that the detection and treatment of neurosyphilitic involvement early in the disease at a time when the preventive value of its recognition is highest, demands systematic examination of the spinal fluid in every case The Cooperative Clinical Group figures bear out this statement in striking fashion. Whereas only 1 7 per cent of 2269 patients with secondary syphilis had clinical signs, 32.7 per cent of 1747 whose fluids were examined, were abnormal

The relation of symptoms and signs to asymptomatic neurosyphilis detected only by examination of the spinal fluid is further indicated in relation to age of infection in Fig 402

Fig. 402.

PROPORTION OF ABNORMAL FLUIDS TO POSITIVE NEUROLOGIC SIGNS

Author	Cases.	Phase of syphilis	Positive fluids, per cent.	Positive symptoms, per cent.	Positive signs, per cent.
Stokes-McFarland	114	Early secondary untreated.	37	16	
Moore	353	Primary and secondary one year	20 8 to 22 1	30	23
Fordyce-Rosen.	213	Late secondary two years.	76	43	64

While due allowance must be made for the many factors influencing the collection of such data, it may reasonably be inferred that the longer the involvement of the nervous system persists, the larger the proportion of patients who show clinical symptoms and signs. The observations of Fildes *et al.* tend to confirm this conclusion. It is evident, therefore, that the detection of early neurosyphilis should not be allowed to rest on signs and symptoms alone, but should be accomplished primarily by a combination of the spinal fluid examination with clinical study This proviso of a combined study brings into the field of diagnosis those patients with unmistakable lesions of the nervous system, affecting especially the cranial nerves, and those with precocious gummatous or vascular changes, who have negative or nearly negative spinal fluids.

Immunological and Mechanical Background of Early Neurosyphilis.—The existing state of knowledge and opinion on these fundamental considerations can be fairly summarized in the following way: the approach of *Spirochaeta pallida* to the nervous system must be by way of the vascular system. The older notion that mere geographic propinquity so to speak, as in extragenital chancres about the face, increases the likelihood of neurosyphilitic involvement is unsupported. The peculiarities of the vascular supply of the nervous system serve, therefore, in the writings of a number of authors to explain many of the clinical features of neurosyphilis. The organisms conveyed to the nervous system by the blood stream are deposited first in the meninges

from which most of the nervous system derives its blood supply Hence, early neurosyphilis is overwhelmingly meningeal and meningovascular in its signs and symptoms. The richest blood supply in the nervous system is t the base of the brain. Basilar meningitis is therefore the fundamental first sign of invasion of the nervous system by *Spirochaeta pallida*, and cranial nerve palsies, optic nerve involvement, headache and increased cell counts on the fluid may be and are, in fact, the expected first signs and symptoms. Later neurosyphilis assumes a distribution for which Gennerich invokes Kafka hydromechanical theories of the distribution of organisms by way of the spinal fluid. The rhythmic pulsation of the cerebrospinal fluid-containing sac under the action of the arterial pulse, tends, as sand is shaken in sifter t distribute solid particles to the most dependent portions—namely the horizontal-lying meningeal floor of the brain base and the most dependent portion of the cord—the roots of the lumbosacral sensory nerves, the spinal root ganglia. This attractive mechanical explanation must not, of course, be expected to cover all observed phenomena. The crypts and funnels about the dural reflections on to the cranial and spinal nerves may however because of their relative inaccessibility and attenuated vascular supply be conceived of as good lurking grounds for organisms. For the vascular supply of the nervous system not only acts as the distributor of the infecting agent, but provides the chief route for the supply of antibodies and medicaments to control the infection once it has been distributed.

It is to be expected therefore, as clinical experience abundantly shows, that while meningeal syphilis is the earliest and most active manifestation of the disease in the nervous system it will likewise be the most responsive to treatment. It is, therefore a very practical maxim that the time to treat syphilis of the nervous system is while it is near the blood supply to which it owes its initial distribution—i.e while it is meningeal. It follows, too, that if relapse occurs in a meningeal neurosyphilis it will be most likely to localize at those points where the meninges are least accessible to protective and therapeutic agents as in neurorelapse and recurrence, which in the large proportion of cases involve the cranial nerves within the meninges. It is important, however to keep constantly in mind that not all early syphilis of the nervous system will bear the meningeal stamp, and that early diffuse and localized involvement of both parenchyma and vessels presents itself in the absence or relative unimportance of meningeal reaction (negative or slightly abnormal spinal fluid)

The balance between infection mass or quantity of organisms present in the body and the resistance aroused in the subject is in all probability one of the most important aspects of the immunological background of early neurosyphilis. It is quite generally conceded that the nervous system is largely dependent upon antibody protection derived from the defense reactions of other structures in the body In other words, it is poorly equipped to defend itself, for the proportion of reacting tissue to more or less inert parenchyma is small. If the character of the infection in the body is such as to arouse sharp defence, as in the development of marked involvement of skin and bones and large viscera, the nervous system is pt t be protected, even though the initial invasion be severe, by copious production of antibodies On the other hand, if the patient shows little general reaction to his infection, even relatively mild invasion of spirochetes may carry neurosyphilitic process through to disastrous termination. In support of these generalizations the apparent immunity of patients with severe late cutaneous lesions and marked visceral changes from pronounced neurosyphilitic manifestations is generally cited. This explanation paradoxically can be applied to the reported greater incidence of neurosyphilis in patients with papular as contrasted with macular secondaries, for the sharper reaction in the former while it does not prevent the initial wave of involvement of the nervous system early in the disease, provides the needed antibodies t overcome it subsequently during the latent period.

While the exact detail of these considerations is far from being worked out, there is no reasonable doubt that it is highly important to keep constantly before one the necessity for conserving and developing the specific resistance of the patient to *Spirochaeta pallida* throughout the early stages of the disease as a protection to his nervous system and not to give oneself too un

qualifiedly to merely spirillicidal attacks on the organism which at their best may so easily fail to reach some difficultly accessible corner of the most vital of structures. It is at this point exactly that the deficiencies of an intermittent arsenical therapy have become disastrously evident, and the comparatively high incidence of neurorecurrence in patients who have been insufficiently treated with heavy metals has occasioned alarm among conservative syphilologists. On the other hand, massive dose arsenotherapy (five-day drip) has to its credit a remarkably low incidence of spinal fluid abnormality. It is the combination of arsenical and bismuth, however, which apparently yields the best ultimate results.

The influence of strains and other protective factors is considered in Chapters I and X.

Sequence of Spinal Fluid Findings in Early Syphilis.—Once the nervous system has been invaded by way of the meninges at the outset of an infection, the succession of events is to some extent reflected in the spinal fluid findings at various periods during the first two years. The first warning of meningeal involvement and reaction is the rise in cell count (Fig. 403) and globulin content. The former, in our experience, is the more trustworthy sign. The Wassermann reaction lags behind as an index of the later parenchymatous extension of the syphilitic process. At first entirely negative, even in the presence of a marked pleocytosis, the Wassermann reaction becomes positive first on large amounts of fluid and finally when a fully developed neurosyphilis is established, strongly positive even on small amounts. The detection of early involvement of the meninges is particularly dependent on a complete examination of a properly drawn spinal fluid, for a slight increase in cell count cannot be recognized if only a Wassermann reaction is done or a blood-contaminated specimen is obtained through faulty technic. The colloidal tests in early cases are often negative, and it is not until the process is fully developed that one obtains the striking first-zone curve that so often marks the severe neurorecurrence, though without necessarily indicating an ultimate paretic outcome.

It is evident, therefore, that on whatever basis the incidence of positive Wassermann reactions on the fluid, globulin increase, and cell count be calculated, the increase in cell count tends to lead the list as the earliest and most conspicuous sign of meningeal reaction, and that the Wassermann reaction lags behind, not reaching its full proportion of positive results until the infection is well established and, in fact, enters upon the clinical recurrent or latent stage after a duration of from one to two years. It is therefore doubly important to insist on accurate and complete cell count reports on the spinal fluids of early syphilis. Nearly 60 per cent of the abnormal fluids in the Cooperative Group's large series showed only a rise in cell count with or without an increase of protein, the Wassermann and colloidal tests being negative.

Relation between the Abnormal Spinal Fluid and the Positive or Negative Blood Wassermann Reaction in Early Syphilis.—The proportion of patients with early neurosyphilis whose blood Wassermann is negative while the spinal fluid is positive is small in the early years of the disease (5 to 8 per cent). The aid afforded by the blood test in detecting neurorecurrence emphasizes an axiom now generally accepted by all who have to deal with early syphilis, that the fixed or relapsing blood Wassermann reaction should always inspire not only cardiovascular study but also a thorough search for involvement of the nervous system, including a spinal fluid examination. It should never be

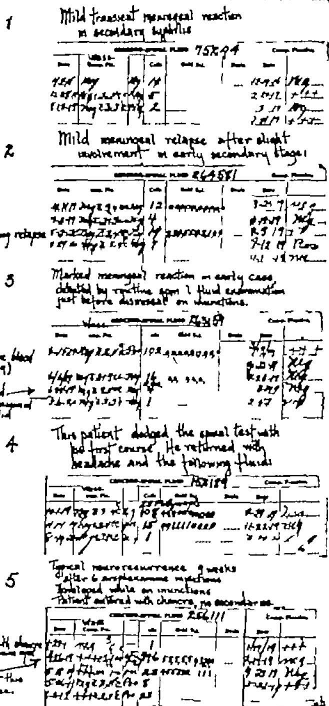


Fig. 403.—Early neurosyphilis. A slight rise in cell count is an important warning of meningeal reaction or impending relapse (see p. 617 Neurorecurrence). It should always be closely watched and treated with special thoroughness.

dismissed as a triviality. In the more recent treatment system formulations for early syphilis, emphasis is laid on the serologic positivity of the blood

persisting beyond the twenty fourth week *as strong evidence of the existence* of neurosyphilis and the need for a spinal fluid examination On the other hand, a *negative* blood and spinal fluid may early in the disease accompany grave neurosyphilitic accidents, especially neuroretinitis (see Fig 405) and vascular lesions of the brain. The Cooperative Group found that there is a definite relationship between spinal fluid abnormality in early syphilis and the blood serologic reaction. The more marked the fluid abnormalities, the more likely is the SWR to be positive. Blood serologic fastness occurs in only 16 per cent of patients with negative spinal fluids. More than 40 per cent of those patients whose fluids showed a positive Wassermann reaction are Wassermann-fast in the blood.

When Shall the Spinal Fluid Examination in Early Syphilis Be Made?— The spinal fluid examination of the patient with early syphilis should not be performed until at least one and preferably two doses of arsphenamine or its equivalent have been administered, to prevent *transfer of infection from the blood stream.*

A spinal fluid examination on every patient with early secondary syphilis during the first two weeks of the first course preferably coincident with the third injection of an arsenical establishes a base-line for subsequent tests, and for the detection of those precocious severe involvements which will demand unusually vigorous treatment. Under the conditions of out-patients city clinic work a compromise with ideal conditions must be made, the fluid being examined toward the end of the first year of *continuous* treatment or before a rest interval is granted. The later the case when first seen, the more important the early examination of the fluid for the type of treatment may depend on it. If the patient with secondaries cannot be induced to accept an early spinal test, the next most essential time for the performance of puncture is the twenty-fourth week in alternating systems before the patient is placed on *subintensive treatment such as bismuth alone. It is during this interval* that any damage to his resistance will make itself felt if the infection has not been completely suppressed. The key to an impending neurorecurrence from a seemingly clear sky can often though not always be found at this time even though there are no clinical symptoms whatever Especial emphasis is to be laid on the slight rises in cell count. The end of the first or second course is the time commended by Moore and Keidel for examination of the spinal fluid because experience shows pretty definitely that the patient who has a positive fluid at this time will require more than ordinary treatment measures to reduce *him to normal. In the foreshortened intensive treatment systems* (five days to twelve weeks) spinal fluid examination between the sixth and twelfth month after treatment begins is advised.

THE CLINICAL PICTURE OF EARLY NEUROSYPHILIS

In Fig. 404 an attempt is made to parallel the pathologic process in the nervous system with the patient's symptoms in each of the recognized forms of early neurosyphilis. The parallelism of this series of clinical lesions with the list of recognized neurorecurrences simply expresses the essential identity of the two processes, as will be explained.

The various lesions tabulated are not at all mutually exclusive, and a diffuse meningeal or encephalitic process may be varied by additional signs of focal involvement, especially of the cranial nerves.

Headache is an important symptom of meningeal irritation in early syphilis, and, *if persistent, calls for a spinal fluid examination on suspicion*. The striking findings which may develop on what seem to be very trifling clues are well illustrated in Fig 541 The group of papules on the palm (lues cornée) was the clue to a meningeal involvement whose expression in headache had sent the patient originally to the gynecologist. The identification of her *ailment brought her husband Fig 414 under observation with his fourth* cutaneous relapse and a resistant neurosyphilis. The moderate grades of meningismus may be mistaken for rheumatic torticollis on account of the stiffness of the neck. Cases with projectile vomiting from intracranial pressure may pass for brain tumor before the blood and spinal fluid are examined.

That there is no necessary correlation between the severity of meningeal symptoms and the cell count in the spinal fluid has been evident in our experience Cell counts as high as 300 to 400 per cubic millimeter have occurred

Fig. 404.

PATHOLOGY AND CLINICAL SYMPTOMATOLOGY OF EARLY NEUROSYPHILIS

Pathologic process.	Clinical symptoms.	Clinical signs.
Basilar meningitis (diffuse)	Headache and head pain, stiff neck, nausea, vomiting.	Fundus examination may show optic neuritis, or choked disk from chiasm involvement or increased intracranial pressure
Basilar meningitis, localized.	Focal symptoms depending on location of lesion (see below)	Focal signs from involved cranial nerves.
Diffuse meningo-encephalitis.	Acut neurasthenia nd anxiety states. Em ti nal d hysterical states. Mental confusion, delirium, maniacal states. Coma, often of sudden onset. Incontinence	Irritative signs, increased reflexes, Babinski sign Paralyses. Loss of sphincter control. Pupillary changes, sluggishness, fixation, inequality Coma. Localizing or focal symptoms from involved cranial nerves.
Acut early syphilitic myelitis.	First symptom usually urinary retention requiring catheter Anesthesia Total paralysis usually of lower extremities with later extension	Wide-spread irritative signs (increased reflexes) followed by sensory *disturbances and* flaccid paralysis.
Syphilitic epilepsy	Epileptiform convulsions	May present Jacksonian or other localizing signs of area involved No residual paralysis.
Early syphilitic apoplexy	Weakness, numbness, or paralysis, arm, leg, opposite side of face	Hemiplegia, usuall partial recovery
Cranial nerve lesions. N VIII (auditory) (cochlear nerve)	Tinnitus, *unilateral or bilat*eral, impairment of hearing, especially for high tones. Ma bear conversation at first.	Lowered *high forks* decreased bone conduction; tone islands. Deafness, partial or complete, slow or sudden, permanent or temporary

Fig. 404 (Continued)

Pathologic process.	Clinical symptoms	Clinical signs.
N VIII (vestibular) Cochlear and vestibular lesions may occur together	Vertigo, nausea, vomiting	Nystagmus, falling t one side, past-pointing. Bárány findings.
N. VII.	None inability to whistle or to close one eye.	Lagophthalmos corner of mouth droops on affected side. Mouth pulls toward unaffected side.
N II.	May be no complaint from slight lesions. Falling vision, scotomata if marked. Symptoms of intracranial pressure in some cases.	Papillitis, exudate; vitreous opacities, central scotoma. Choked disk.
N III.	Diplopia.	If partial, may be only weakness of internal rectus. Nuclear paralyses may affect only extra-ocular muscles. Total paralysis produces ptosis, outward deviation of eyeball, face upward and toward one side, head inclined to shoulder of paralyzed side. Slight exophthalmos, pupil dilated and fixed. Accommodation paralyzed.
N IV	Diplopia.	Eye deviates upward and slightly inward. Face directed downward and toward sound side. Limitation of movement downward and toward paralyzed side.
N VI	Diplopia.	Convergent squint, face turned toward paralyzed side. (External rectus paralysis.)
N V	Anesthesia, sometimes with some preceding neuralgia, over areas innervated by this nerve. Corneal disturbances. Cheek biting.	Anesthesia over areas supplied, including conjunctiva and palate Paralysis of muscles of mastication. Neuroparalytic keratitis.

in patients with no symptoms. Zimmermann calls attention to the fact that a high cell count may be produced by a focal lesion without general involvement of the meninges. The symptomatology of the meningo-encephalitic and vascular lesions is described in Chapter XX.

The Influence of Treatment Upon Early Neurosyphilis. Therapeutic Shock vs. Neurorecurrence.—An acute process in the nervous system undetected, and treated abruptly with arsphenamine, gives rise to symptoms from the affected group of structures which should be classified as Herxheimer reactions. These Herxheimer reactions may develop upon subthreshold processes, as in the case of a clinically inconspicuous involvement of the eighth nerve, for example, and may result in serious and permanent damage. Sudden deafness, *a period of coma, convulsions, seventh nerve paralysis, may all* follow the first injection of arsphenamine in a patient whose neurosyphilis

Fig. 405

OPTIC NEURORECURRENCE WITH NORMAL SPINAL FLUID AND BLOOD FOLLOWING INSUFFICIENT ARSPHENAMIN TREATMENT. RAPID RECOVERY AND APPARENTLY COMPLETE CURE. REINFECTION (?) (PRIMARY AND SECONDARY LESIONS) FOURTEEN MONTHS AFTER FIRST EXAMINATION. SECOND REINFECTION (?) FOUR YEARS AFTER FIRST EXAMINATION

Laborer aged thirty-two years.

7/24/20 Examined.

History of Penile Lesion with secondaries six months before.

History of Treatment: Five intravenous arsphenamin injections and potassium iodid by mouth, no mercury.

Vision Began to Fail one month after last arsphenamin injection.

Eye Examination: Violent rapidly progressing neuroretinitis.

Physical Findings negative.

Wassermann Reaction on the Blood negative.

Spinal Fluid negative.

Diagnosis: Neuroretinitis, probably syphilitic.

Rapid Improvement under mercury succinimid and iodid, followed by arsphenamin.

Further Treatment: Four arsphenamin courses as for an early infection. Forty injections of mercury succinimid, 200 4-gram inunctions, 345 gm. sodium iodid intravenously.

11/22/21 Re-examined. Multiple penile lesions developing two weeks after drunken spree.

Physical Findings: Several scattered papules on penis of several weeks duration.

Induration of Old Scar: No erosion or other sign of activity.

Spirocheta pallida demonstrated eight days after examination *in small penile lesion*.

Wassermann Reaction on the Blood strongly positive.

Maculopapular Secondaries on Trunk and Arms Appeared Twenty Days After Examination.

Wassermann Reaction on the blood again strongly positive.

Condition of the Eyes: Normal except for organized exudate of healed neuroretinitis.

Spinal Fluid negative.

12/27/21 Was Seen with Chancre of the Cervix.

9/27/23 Slight serologic relapse (Kolmer 21) spinal fluid normal. One month later negative.

7/21/24 Eight months later penile lesion (5d) followed by typical macular secondaries.

Discussion

1. *Grave Involvement of a Cranial Nerve* in the neurorecurrences of early syphilis may be associated with a negative Wassermann reaction on the blood and negative spinal fluid.

2. **It Is Remotely Conceivable That the First Neuroretinitis Was Nonspecific,** but its rapid response to mercury succinimid and iodid with the history would seem to establish the first syphilitic infection.

3. **Was the Second Infection a Relapse (Monorecidive), a Reinfection or Superinfection?**

The induration of the old primary scar suggests a relapse. On the other hand, spirochetes could not be found in this induration, but they were demonstrable in one of the chancres at a distance from the original lesion. While specific exposure was denied, the patient had been drunk and irresponsible at approximately the proper time for a new infection to have occurred. It is not possible however to state categorically that this is not a primary relapse with a second crop of secondaries.

4. **Reinfection Cannot Be Proved** without more definite history of exposure and chancre less obviously in the immediate neighborhood of the original primary.

5. **A Superinfection is Easily Conceivable** but not probable in this case.

6. **The Course of the Second Infection Has Been Very Different from the First.** No tendency to involve the optic nerve is thus far apparent.

7. **If This is a Relapse of the Original Infection** the original involvement of the optic nerve (neurorecurrence) would scarcely appear to be due to a neurotrophic strain of organism, but rather to the effect of insufficient treatment (especially lack of mercury as such).

8. The second "reinfection," in view of the previous serologic relapse suggests recurrence but may be a superinfection.

has not been detected by careful history and examination and provided for by heavy-metal preparation. Such accidents are hardly to be regarded as neurorecurrences in a strict sense though expressive of kindred neurosyphilitic lesions. They can in the majority of cases be avoided by proper study of the case before treatment is begun, and an intelligent and cautious initiation of treatment.

Neurorecurrence. An Effect of Inadequate Treatment.—Neurorecurrence is not to be confused with a therapeutic shock or Herxheimer reaction, nor is it to be regarded as evidence that "arsenic" has "predisposed" the nervous system to spirochetal invasion. It is merely a sudden relapse of an imperfectly extinguished infection in a structure peculiarly inaccessible and difficult of sterilization and in a patient whose resistance has been prevented from developing by improper treatment. Neurorecurrence may assume all of the clinical forms of early syphilis of the nervous system. Its relation to arsenical therapy is discussed in Chapter V The remedy for neurorecurrence is more intensive treatment for syphilis, better directed in that it always employs both spirillicidal and resistance-building therapy coincidently or in immediate succession to one another and does not place the patient with early syphilis on prolonged rest periods or dismiss him from observation and treatment after a few injections of arsenical.

The definition of "neurorecurrence is by no means easy matter and assumes some importance in view of the polemic discussions, especially between Harrison and Burke dealing with the relative merits of alternating and simultaneous use of arsphenamines and heavy metals in early syphilis. Strictly and originally neurorecurrence is sudden isolated clinical manifestation or injury appearing after lapse in treatment, early in the disease, and usually involving the vascular or cranial nerve mechanisms in hemiplegia or palsy This definition takes no cognizance of what might be thought of as serological neurorecurrence, in which previously normal spinal fluid is found on subsequent examination after lapse, to show marked abnormality often of the "red flag or preparetic type, even though no clinical symptoms accompany the relapse. If the range of spinal fluid abnormality in such recurrences be extended to include all abnormal fluids, even with slight rises in cell count, the proportion of neurorecurrence will evidently appear higher than in current estimates based purely on symptomatic criteria. Thus, when an observer states that he has never seen neurorecurrence, it is necessary to know what he means by neurorecurrence. The narrower or older definition is the more widely used, the serological relapses tending to be ignored through nonuse of spinal fluid examination in certain clinical materials (e. g British), or being rated as "neurosyphilis progressive in spite of treatment. There is, too, tendency to use figures dealing ith serological neurorecurrence to illustrate contentions based on clinical neurorecurrence. W personally tend to define neurorecurrence or neurorelapse as either clinical or serological revival or outburst of nervous system involvement after lapse in treatment preceded by clinical serological (spinal fluid) normality In view of the obvious difficulty in defining the borderline of involvement in the nervous system when spirochetes may be present in an apparently normal fluid, it is probably too soon to attempt final classifications and definitions distinguishing neurorecurrence from early neurosyphilis in general.

Zimmermann, from study of the experience of the Johns Hopkins Clinic, estimates the frequency of clinical neurorecurrence at 1.8 per cent in 1400 patients with early syphilis on service which uses arsphenamine and mercury in alternation. The Cooperative Clinical Group found 2.9 per cent neurorecurrence in 3444 cases of early syphilis under observation for more than six months. Gennerich estimates that 10 per cent of those who develop meningeal neurosyphilis in the first year will show outspoken neurorecurrences. This places clinical neurorecurrence among the comparative rarities of even special practice. The frequency of the general forms of neurorelapse is indicated by Gennerich as follow r of 9 cases with general symptoms, 4 had epileptiform attacks, 3 had severe headache, and 1 each had coma (encephalitis?) and apoplexy Of the forms involving cranial nerves Zimmermann gives comparative table (Fig. 406) including his own results and Gennerich s.

Onset of Symptoms.—As a rule the onset of symptoms in neurorecurrence as in primary symptomatic neurosyphilis is sudden, but may be very gradual.

The earlier stages may not be apparent either to patient or physician. The predominance of auditory and facial nerve involvements, and combinations of the two, is apparent from the figures. The symptomatic optic nerve lesion

Fig. 406.

CRANIAL NERVE INVOLVEMENT IN NEURORECURRENCE

Nerves involved.	Zimmermann.	Gennerich.
Optic.	3	1
Oculomotor	1	
Trochlear	1	
Trigeminal		1
Facial	3	4
Auditory	4	6
Facial and auditory	10	2
Oculomotor and facial	1	
Trigeminal and facial	1	
Oculomotor and trigeminal	1	
Optic facial and auditory		1
Oculomotor and abducent.		1

is, of course, much less frequent than the asymptomatic papillitis, but may cause remarkably rapid failure of vision.

Neurorecurrence in Untreated Patients and Those Receiving Only Mercury or Bismuth.—It is entirely possible for a neurorecurrence to develop

Fig. 407

EARLY TREND TOWARD GRAVE NEUROSYPHILIS

Man, aged twenty-five, railroad.

Chief Complaint Penile lesion sixteen days duration with bubo.
Syphilologic Examination Darkfield positive, serum Wassermann positive.
No secondaries. SWR ###
Cerebrospinal fluid. (with second injection arsphenamin)
WR negative Nonne negative; 1 lymphocyte.
Eight weeks later after 6 injections and 55 inunctions
Cerebrospinal fluid. WR ### Nonne ### lymphocytes 406.
Lange 5555543210 SWR negative; five weeks later after 7 injections and no inunctions (patient had been drinking and not co-operating)
Cerebrospinal fluid WR ### Nonne ## lymphocytes 25 Lange 5555320111 SWR ###

Comment At this point the patient disappeared from observation. On reporting him by name to the State Board of Health, he was obliged to resume treatment under a private physician, but no opportunity was given us to advise the physician of the gravity of the case.

Every Physician Who Takes Over a Case Treated Elsewhere Should Ask for and Receive a Full Report of the Findings of His Predecessor

Note—Six years after the last examination of the spinal fluid, without interim treatment, this patient appeared in the clinic with general paresis.

in an untreated patient whose infection is following the ebb and flow of his own defence mechanism It was well known under mercurial therapy in the prearsphenamine era. It has been observed under an exclusive bismuth

therapy as in the Breslau Krankenkassen "epidemic" (Hugo Müller) The term as previously noted may quite as properly be applied to flare-ups of asymptomatic meningeal neurosyphilis in patients who have previously been shown to have negative spinal fluids, as in Figs. 407 456

Prognosis of Neurorecurrence.—The prognosis of the early neurosyphilis with symptoms and of the symptomatic relapse of neurosyphilis varies with the structures affected. That of the eighth nerve, as studied by Alexander is good for the mild type which presents only tinnitus, slight diminution in hearing, and spontaneous nystagmus without vertigo. The prognosis of pure vestibular involvement is good, but 30 per cent lose the function of the static labyrinth. Marked cochlear symptoms, and a sudden severe onset have a bad prognosis for recovery of hearing. The outlook in optic neuritis, if the process has not been too long neglected is good, and remarkable recoveries of vision follow the institution of effective treatment. Seventh nerve lesions are more refractory and partake of the prognosis of eighth nerve lesions.

Unfavorable Reactions in Early Neurosyphilis.—Stokes has been able to watch both symptomatic and asymptomatic neurorecurrence appear while the patient was on reasonably effective arsphenamine or heavy metal therapy Such cases may perhaps best be regarded as 'progression in spite of treatment."

One patient, while on large inunctions following 8 injections of arsphenamine, developed combined seventh and eighth nerve lesion. Another developed full-fledged meningeal neurosyphilis while actively under treatment with arsphenamine. Still another comparatively late case, was made definitely and rapidly worse by arsphenamine and was only controlled by huge dosage of mercury by inunction and iodides by mouth and intravenously There is unquestionably type of meningeal flare-up which can be provoked into activity by injudicious prodding of a seemingly quiescent case with arsphenamine, sometimes to subside again when the drug is pushed or others substituted. All these considerations indicate that the problem of neurorecurrence is not simple one, dependent merely on one factor such as the inadequate use of arsphenamine. There seems at times to be definite and even irresistibly unfavorable trend, and not even treatment effectively given can always stop it. Heavy-metal treatment is, of course, most valuable as builder of the systemic resistance which prevents neurorecurrence, but it cannot be offered as an absolute preventive.

Occasionally a case will appear in which the arsenicals will evidently be entirely out of place in the therapy and under such circumstances heroic bismuth, mercurial, and iodide therapy hard though it may be for the patient, may be necessary to control the situation. A resort to fever therapy in such cases may be particularly helpful (O'Leary)

Precocious Tertiarism in the Nervous System.—Precocious tertiarism the allergic response of tissues in the early stage of syphilis, which results in gummatous lesions years before their expected period in the chronology of the disease, may occasionally be seen in early syphilis of the nervous system For example, J.H.S. has seen a case of brain gumma with negative spinal fluid develop within the first year of a fairly well treated infection. The vascular accidents, reported as early as three months after infection (Gennerich) are very possibly precocious gummatous and thrombotic involvements of cerebral vessels.

Ultimate Prognosis.—The ultimate prognosis of early neurosyphilis can not as yet be exactly defined, for one has only to observe its possibilities for relapse and for symptomatic progress without serological signs over a period of years to realize that there are no criteria of cure on which complete reliance



Fig. 408.

ANESTHETIC RASH"

Woman, aged twenty-six, married, telephone operator

Note the small horny papular lesions in the centers of these palms and t the flexures of the fingers. The center of each palm was markedly erythematous ith scattered patches of deeper color nd with the more easily visible horny lesions superposed. The patient gave the following history

A year nd three months before coming to the clinic large bluish lumps had p peared in both groins These lasted approximately tw months, nd then the patient went to hospital t seek relief for general ill health. She wa xamined and told that an operation wa necessary which was then performed. The patient describes it as "right ovary pack and adhesions. The lumps subsided rapidly after operation.

Approximately two days after the operation measle-like eruption broke out, first ver the arms, then over the entire body The patient inquired as t its nature and states that sh was told it was an 'anesthetic ash. Her convalescence as otherwise uneventful, but after she left the hospital her mouth became sore. She went t the surgeon ho had performed the operation for relief and states that he ished t treat her mouth ith nitrat of silver In view of the fact that she had mucous patches in the commissures hen she examined at the clinic it seems probable that this part of her secondary manifestations. She later saw her home physician, who urged her t have her tonsils removed. Coincidently ith the ppearance of the mouth lesions the eruptive lesions on the palms also developed and ere present to varying degree throughout the following eight or nine months

During the year that she pparently having secondaries on the skin, mucous membranes, nd palms this patient seen by 3 surgeons and 1 general practitioner She as not given an thing that would suggest systemic treatment for syphilis, she did not receive ny diagnosis, nd so fa could be ascertained from the patient account no diagnosis made Inquiry t the explanations offered for the various lesions present elicited the reply "They used to pinch my hands this y and said just your condition after operation So far can be ascertained nobody suspicion was aroused t the point of taking W sserma reaction at any time

Upon examination in the clinic in ddition t the palmar lesions, involuting mucous patches ere found from which no spirochetes could be obtained, and the W sser mann reaction on the blood strongly positive The spinal fluid findings ere as follow

Wassermann reaction strongly positive with 0.4 0.6, and 1

Nonne positiv

100 small lymphocytes.

20 large lymphocytes

can be placed. The tabular summary of prognostic grading of spinal fluid findings gives a close practical approximation to the type of case in which a given type of treatment may be expected to produce a satisfactory result (Chapter IV) The question is often raised, and has usually been answered in the affirmative by such observers as Fordyce and Wile, as to whether the patient who seems to have escaped involvement in the earliest months of the infection can confidently hope to remain free of neurosyphilis throughout the course of his disease. We have ourselves taken this view in earlier studies, but with increasing qualification as we note the development of late serological relapse in both blood and spinal fluid in patients protected seemingly by every resource of modern treatment, including pregnancy An illustration of such a case is shown in Fig. 435 Lomholt (1036) Livingood and Beerman (1941) and Kopp and Solomon (1941) have supplied further clinical evidence in support of this position. The question as to whether a patient who has acquired syphilis can ever be released from the need for a periodic examination of the nervous system and the spinal fluid test, like the entire problem of the extent and character of observation in seemingly arrested syphilis, cannot be conclusively answered at this time. Moore's observations for the Co-operative Clinical Group indicate that once true latency is attained a negative spinal fluid need not be reexamined more than once, if at all. The tendency under war time pressure is increasingly to dismiss as permanently recovered and free from risk of neurosyphilitic relapse patients who following adequate modern treatment in early syphilis or the achievement of latency in later syphilis, have obtained a negative spinal fluid examination. To this statement we would certainly add the exception that the recurrence of a positive serologic test on the blood or the intervention of trauma (head trauma especially) should call for a reexamination of the spinal fluid.

Fig. 408.

TO DETECT EARLY SECONDARY SYPHILIS

1. Properly follow up all doubtful genital lesions.
2. Strip the patient for examination. See everything in good light.
3. Expect symptoms in women, signs in men.
4. Trust the blood serologic reaction, but don't call everything syphilis in the patient whose blood serologic reaction is positive.
5. Use the darkfield carefully if there are vailable lesions.
6. Accept the repeatedly negative blood serologic reaction as eliminating all but 1 per cent or less of eruptive secondary syphilis.
7. Be more suspiciously minded gynecologist or otolaryngologist. Use the blood serological test routinely
8. Know the clinical characteristics of secondary syphilitic lesions.
9. Take more blood serological tests on young adults ith headaches, persistent sore throats, "rheumatism," and pseudotuberculous symptoms.
10. Keep early neurosyphilis always in mind.
11. Give your patient summary of your findings in writing when or before he goes to another physician, to supply the evidence for his diagnosis when his signs have vanished.

CHAPTER XIII

THE CLINICAL ASPECTS OF RELAPSE, REINFECTION AND PROGRESSION IN EARLY SYPHILIS

The Importance of Relapse.—Syphilis, as we have already remarked is the relapsing disease par excellence The ability to recognize relapse, to know when and where to look for it, to understand its influence on the transmission of the disease, and to control it, becomes an essential part of the equipment of every physician who assumes charge of a syphilitic patient.

The literature of relapse is still obscured and study of the subject retarded by an over shadowing interest in the subject of reinfection, due largely to the bearings of the latter on the question of cure. The subject of early infectious relapse is one of great practical importance, for the maintenance of infectious foci through relapse in improperly treated early syphilis is undoubtedly an important bar to the conquest of the disease. Mucocutaneous relapse in particular stands in a numerical ratio of 1 to 16 to early syphilis itself as disseminator of the disease. It is one fifth as important numerically as the chancre among infectious lesions, while reinfection is only one fifty-seventh as important as the chancre numerically in the potential transmission of syphilis.

The immunological relations of relapse and reinfection have been discussed in Chapter I They should be reviewed as a preliminary to full under standing of the relapse problem

The Forms of Relapse.—The physician should be on the lookout, especially in the earlier years of his patient s infection, for one or more manifestations of the following relapse categories.

1 **Mucocutaneous relapse.**

2. **Serological Relapse.**—These two exceed all others in frequency and constitute, according to the large material of the Cooperative Clinical Group, 12.1 and 15 1 per cent respectively of the total number of early cases studied and under treatment for six months or more (5244)

3 **Ocular recurrences** (3.3 to 0.3 per cent depending on method of treat ment) include iritis, iridocyclitis, keratitis, neuroretinitis. The form of ocular relapse seen most often in Negroes is iritis.

4 **Neurosyphilitic relapse** either in the form of neurorecurrence in the strict sense (see p 017) (2.9 per cent) or of asymptomatic neurosyphilis develops following a previous normal spinal fluid (3 4 per cent)

5 **Bone and joint lesions** (0 4 per cent) as forms of relapse, include particularly periostitis and osteitis. Headache for example, is not infrequently (especially in Negro patients according to Moore) an expression of cranial osteitis as a form of relapse.

6 **Visceral lesions** (0 05 per cent) especially hepatitis.

7 **Birth of a syphilitic child** to an apparently healthy and serologically negative mother who has syphilis.

8 **Infection of a sex partner** with syphilis in the absence of detectable clinical or serological relapse in the patient.

The relative frequency of these forms of relapse can only be partly estimated but the percentage data given here from the Cooperative Clinical Group investigation are believed to be representative.

Mucocutaneous Relapse.—This particular field of relapse, in many respects the most important of all, especially from the standpoint of the public health, has been specially studied in the University of Pennsylvania Clinic by Besancon, Schoch, Ireland and Stokes, by the Cooperative Clinical Group and by Kern. The following summary is drawn largely from the first two sources.

Statistical estimation of the incidence of infectious recurrence and mucocutaneous relapse is influenced greatly by the stage of syphilis represented by the material under consideration. For example, if patients under observation for less than six months are excluded, it was found in the Cooperative Clinical Group surveys that the proportion of mucocutaneous relapse to the total of cases was materially affected In the collected material of this group among 5952 cases, regardless of observation period, mucocutaneous relapse occurred in 6.05 per cent of patients, 86 per cent of them relapsing once 11 per cent twice, 2 per cent three times and 1 per cent four times. In patients observed for six months or more, the incidence was 12 1 per cent. Infectious relapse is more frequent in males than females, and in Negroes than in white patients. The Negro woman in particular is conspicuously a subject of infectious relapse.

The frequency of relapse is influenced by the age sex and color of the patient, the age of the infection, the stage of syphilis at which treatment begins, the mass of treatment received the system of treatment (simultaneous versus alternating) and the prolongation and scheme of treatment employed. Relapse tends to be more frequent in the younger patient (33.3 per cent for patients under sixteen years and 30.9 per cent for patients between sixteen and twenty years as compared with 23 per cent in patients over forty) The influence of the age of the infection is of great importance not only in the control of infectiousness in patients themselves but in the differentiation of relapse from reinfection. Within the first six months of the infection, 25 7 per cent of relapsing patients have relapsed, and in the second six months 29.2 per cent, making a total of 54.9 per cent within the first year (Cooperative Clinical Group) By the end of the second year after infection, 84 7 per cent of relapsing patients have relapsed. In relation to treatment, 45 per cent of relapses occurred within six months after treatment was stopped, 73 6 per cent by the end of the first year 91 per cent by the end of the second year Thus it is evident that infectious relapse is largely concentrated into the first two years of the infection or after the cessation of treatment. The Cooperative Clinical material included 33 cases in which relapses occurred from three to seven years after infection and eight instances of relapses more than seven years after infection. Relapse may occur as early as three weeks after the onset of the infection.

The most widely quoted figures on the time of onset of cutaneous and mucosal relapse are based on the transmission of syphilis in marriage in the prearsphenamine era. Fournier found that 84 per cent of women were infected in the first three years of their husbands' disease, and 66 per cent within the first year. Tschestjakow from Tarnowski' clinic, is quoted as finding 80 per cent of relapse within five years in 1000 patients· 16.7 per cent within the fifth to the tenth years; 2.8 per cent in the tenth to the fifteenth years; and 0.5 per cent in the fifteenth to the twentieth years. Gennerich, in 1914 in 30 patients receiving so-called abortive cures, noted 5 relapses within one year and regarded 5 additional cases as reinfections. Gennerich and Zimmern, in reporting long series of reinfections, observed monorecidives or relapses of the chancre as early as thirty-one days after the seventh injection of arsphenamines. Gennerich also found in 30 patients with early secondary syphilis, 40 per cent had recurrence of the disease in from one and one-half

t three years. Hudelo and Rabut noted in their series of 51 monorecidives that 63 per cent appeared within the first year and from that point on the percentage occurring in successive years fell from 20 in the second year to 2 per cent (1 case) in the sixth and seventh years respectively Caesar observed a monorecidive three years after the first chancre which, while not in the same site, was in the same lymphatic drainage. The most delayed monorecidive in our experience was recurrence on the finger five years after primary lesion in that site, followed by the development of an ulcerative sore throat five weeks later

Various forms of relapse of the secondary eruption have been observed at varying intervals. Saenz reported maculopapular eruption with a monorecidive or recurrence of the chancre three months after the original primary lesion, following 6 injections of neoarsphenamine and 6 of an arsenic and mercury preparation. Barbacci observed recurrent roseola seven months after 12 injections of neoarsphenamine. W have observed delayed or recurrent secondaries from four months to four years after suspension of treatment begun in either the primary or the secondary stage. Infectious recurrences in the mouth have appeared in our experience as lat as eleven years after infection, and Nielsen reported finding *Spirochaeta pallida* in what appeared to be recurrent lesions nine years after infection. Pariser (1930) found six cases of infectious relapse occurring two and a half or more years after onset of infection among 120 cases encountered in our University of Pennsylvania Clinic from July 1, 1937 to December 31 1938. One of the six had relapse ten years and nine months after the infection was first discovered and another had a recurrence of infectious lesions six years and four months after her original infection. There was no evidence of reinfection in either case. Kern (1941) observed seven relapses in cases, adequately treated, *from three to eight years after infection among 81 patients with infectious relapse at*

Fig 410

CONTAGIOUS SYMPTOMS TEN YEARS OR MORE AFTER SYPHILITIC CONTAMINATION 2,856 OLD SYPHILITICS*

	Cases
10 years	14
11 years	14
12 14 years	14
15–27 years	12
Total	53

From Felix Pinkus, Urol. & Cutan. Rev 1912.

the Vanderbilt University Hospital Clinic One-third of his cases relapsed less than six months after the last treatment, two-third relapsed ithin one year after cessation of treatment, and only 17 per cent relapsed more tha t years after treatment. Pinkus (1912) found 2 per cent of 2,856 Berlin women had infectious lesions (containing spirochetes) ten or more years after thei infections. (Fig 410.) The percentage rose t 4 if one considered only the period seven years after infection.

The American figures of Moore and Kemp compare very closely with our own t the time of relapse in cutaneous and mucosal lesion in early syphilis. These uthors, in 85 cases (our series 56 cases) found that the erage lapse from treatment was 8 1 months (University of Pennsylvania *series 8.5 months*) W *observed t recurrences in the second month. They found* comparatively few before the third month.

In our Pennsylvania series 24 per cent relapsed in the first six months after onset of the infection and 31 per cent in the second six months, making total of 55 per cent within the first year of the infection and 93 per cent before the end of the second year of the infection.

Duration of Noninfectiousness.—It would appear from the foregoing figures that noninfectiousness, at least so far as it concerns cutaneous and mucosal relapses, has an expected duration in perhaps the first year of the disease of from one to two months after cessati n of treatment. No such figures, of course, can be absolute for we have in our series a patient whose chancre during a two-weeks lapse from treatment after seven injections of bismuth arsphenamine sulphonate, recovered its trde and grew mightily

The great danger of infectiousness from relapse falls in the first two years, and modern treatment has not apparently modified this established dictum materially for those patients who receive too little of it or who, for reasons not as yet apparent, are predisposed to relapse. The "safety period" after a trivalent arsenical then, if such exists at all, is perhaps one to two months and



Fig. 411.

RECURRENCE OF MEATAL CHANCRE (MONORECIDIVE) ONE MONTH AFTER ONE ARSPHENAMIN INJECTION

Male, aged forty-one married, miner

The lesion consists of an induration about the meatus slightly raised and superficially eroded. Marked inguinal adenitis.

The patient gave a history of a primary lesion developing nine or ten days post coitu at the site of the present recurrence. His physician made a darkfield diagnosis, told him he had syphilis, instructed him in regard to treatment, and gave him his first arsphenamin injection. The lesion immediately cleared up and the patient did not report for further treatment.

One month later the lesion reappeared, and the patient, in a panic, came to the clinic.

There were no signs of secondaries. The Wassermann reaction was *negative* and has always remained so during three years of observation and treatment.

By darkfield examination a few spirochetes were demonstrable in the recurrent chancre. Enormous numbers of exceedingly active organisms were obtained by glandular aspiration, from the inguinal bubo.

Discussion.—There is no intrinsic reason why a syphilis incompletely aborted should not start over again from the beginning, or repeat any individual stage or succession of stages.

The darkfield examination of infectious relapses is often more valuable than the Wassermann test in making or confirming the diagnosis. Note that this patient has never had a positive Wassermann reaction and that aspiration of the glands eliminates saprophytic spirochetes, so that the patient had an undoubted early relapsing syphilis.

is not to be relied on when as in marriage, an infected partner may desire to resume unprotected intercourse or habitual intimate contacts during rest periods, either as a matter of preference or with conception in view

The Forms of Mucocutaneous Relapse.—The recurrence of the chancre in situ, called a "monorecidive" (Fig 411) is the simplest and usually the earliest form of relapse It is often spoken of loosely as "chancre redux," a

term which is undesirable because of the ease with which it is confused with the pseudochancre redux, the long-familiar term for the gummatous recurrence at the site of a primary lesion many years before. The monorecidive or recurrent chancre may ape in every particular the primary lesion of the disease. It may be accompanied or followed by a revival of the satellite adenopathy and it should contain *Spirochaeta pallida* demonstrable by dark field if it is to be completely differentiated from pseudochancre redux. A local reaction at the site of the chancre without the actual complete recrudescence of the lesion may accompany the recrudescence of secondary manifestations of the disease. The ease of confusion of the monorecidive with the chancre of reinfection is attested by the practically universal acceptance of the criterion, and a reinfection to be credited as such must not occur in the site of or in the lymphatic drainage of the original primary lesion.



Fig. 412.—Mucous Membrane Recurrences in Spite of Treatment. Beginning Leukoplakia.

A, Active mucous patch near left labial commissure. This is common site for such lesions.
B, An involuting mucous patch of the lip in the same patient entirely concealed until the lip is everted. A faint, silvery leukoplakia is developing about the lesion. The patient own fingers are controlling the lip, which should not be touched by an examiner with ungloved hands.

The chancriform solitary indurated papule or giant papule mentioned in the reports of Gennerich and Zimmern, Hell, Hudelo and Rabut, and Balzer is a papular recurrent lesion entirely outside the zone of primary involvement, and in many cases, at least, to be interpreted, we believe, as a lesion of the secondary stage, even though its appearance is identical with that of the primary lesion. Balzer includes the chancriform papule with the monorecidive under the term of pseudoreinfection and this term is adopted in Bernard's summary of the subject of reinfection.

Secondary recurrences which either chronologically or morphologically mimic the lesions of the early secondary stage in the normal evolution of the disease, form the next group of relapse lesions. They are rarely confused with the lesions of reinfection except in those cases in which the size and erosion of a single papule in an appropriate site give the impression of a chancre with its ensuing secondaries. The fact that such a papule may not be erosive and hence may give the impression of a late and partially healed primary lesion



Fig. 413.—An eroded mucous patch on the under surface of the upper lip in a patient with an unrecognized and untreated syphilitic infection. The patient spat spirochetes while a submucous resection was performed before the lesion was recognized. The postoperative blood Wassermann reaction was strongly positive.



A B

Fig. 414.—Scrotal mucous patches and papular syphilid of the sole of the foot three years after infection in a "supposedly cured" case.

The chancre was apparently diagnosed by inspection without darkfield or Wassermann test and the patient was given 10 arsphenamine injections with complete involution of lesions.

First Relapse.—Scrotal recurrences four months later. Wassermann positive, spinal fluid not examined. Lesions disappeared under another course of 10 arsphenamine injections, 5 intramuscular mercurial injections, and 20 inunctions.

Second Relapse.—A year later the second relapse occurred and he was given 5 neoarsphenamine injections at five-day intervals.

Third Relapse.—Four months later an eruption appeared on the scrotum and soles of the feet, accompanied by sore throat. At this time the patient asserts that his physician told him it was impossible for him to have syphilis because he had been adequately treated for it.

This eruption and the mucous lesions were seen in the clinic three months later. At that time he had mucous patches at the upper poles of both tonsils; the lesions shown in the photographs; mucous patches on the scrotum from one of which *Spirochaeta pallida* was recovered (A); a strongly positive blood Wassermann reaction, and a spinal fluid with a strongly positive Wassermann reaction 0.2 and 1 cc., positive Nonne and 6 lymphocytes, colloidal test negative.

The discovery of this infectious relapse is to be credited to the follow-up system. This is the typical course of the mucous relapser. No physician need feel any hesitation in diagnosing syphilitic recurrences merely because the patient has had prolonged and energetic treatment. Part of the eruption on the sole is trichophytic (organism found in vesicle top). The syphilitic part vanished under treatment.

with active secondaries, increases the possibilities of confusion. Secondary recurrences appear as mucous erosions or patches (Figs. 412, 413 414) as



Fig. 415.—An illustration of the triviality of cutaneous recurrences.



Fig. 416.—Scattered annular lesions in relapse following 30 neoarsphenamine injections and several courses of mercury salicylate injections. The patient had been discharged as cured. The relapse developed within thirty days. There as no evidence of reinfection.

moist papules and condylomas as dry papules in erodable sites (Fig 417) as macular papular (Figs. 415 416 417 418 419 420) annular (Figs. 418 419 420) pustular grouped follicular and corymbose lesions (Fig 421) and as

alopecia. The later recurrent secondary lesions tend toward destructive characteristics, though destructive characteristics may be likewise the result of a premature allergy induced by *insufficient treatment (Fig 423) It is,* of course, conceivable that any of these groups of lesions may be expressions of a superinfection without primary manifestations, a possibility still theoretical for man.

In addition to the monorecidive, the chancriform papule and the secondary recurrence, it is possible to include in discussion of relapse the so-called delayed generalized secondary manifestations, which include the appearance from



Fig. 417—Dry Papule of the Penis—A Potentially Infectious Recurrence.

The mucous surface of this papule was the thinnest imaginable without actual erosion. The lesion was associated with similar recurrences of the scrotum (Fig. 416) and mucous lesions in the mouth.

The primary infection in this case occurred in November, 1918, although he gave history of supposed syphilitic infection sixteen years ago.

At the time of his first appearance in the clinic he had tremendous outburst of mucous lesions, papular secondary lesions, and apparently precocious gumma of the nasal septum as relapse following 6 arsphenamine injections and mercury by mouth. He responded promptly to another 6 arsphenamine injections and then disappeared from observation. Nine months later he took 3 more injections and again disappeared. Six months after his second disappearance he returned with the scrotal recurrences here illustrated, and with mucous lesions in the mouth. During his lapses in treatment he had evidently had repeated herpetic and moist lesions and had developed syphilitic laryngitis with an ulcer of the false cords.

This is the typical course of an infectious relapsing type of case. It is particularly alarming and serious defect in the inadequate treatment methods so often applied to early syphilis, that the symptomatic response is so striking that the patient as ell as the physician is entirely thrown off guard, and the patient sometimes sustains an almost indefinite prolongation of his infectious recurrent period t the grave danger of the public. Only systematic examination will disclose lesions of this sort. They are practically symptomless.

a clear sky in a previously treated and apparently latent or "cured" case, of the extensive outburst of secondary manifestations which should have formed part of the clinical picture or progression of the disease months or years before. Delayed secondaries are, then, essentially a subdivision of secondary relapse, in which the first crop of secondary lesions failed to appear They may be regarded in a sense as lesions of progression in spite of treatment, rather than of relapse. This brings out the fundamental essential of any working definition of cutaneous and mucosal relapse, which is *an appearance or reappearance of lesions after treatment has been suspended* Without previous treatment, relapse

for the purposes of general definition does not exist all other lesions being regarded as progression



Fig 418.—The Annular Scrotal Recurrence.

This is classical picture of type of recurrence relatively unfamiliar because of the omission of routine inspection of the surface of the scrotum in many examinations. When dry the lesion is fleshy with little or no scale. The appearance of scale in the photograph is due to wrinkling of the shiny slightly indurated border This is the same patient described in connection with Fig. 417 The Wassermann reaction t this time was positive. The possibility of annular lichen planus and annular psoriasis should not be overlooked in differential diagnosis in the presence of negative Wassermann reaction.



A B

Fig 419 —T see an annular recurrence on the scrotum, it is necessary t *put the skin on stretch*. This patient was treated by an army technic pparently told he wa cured, married, and infected his wife.

The Localization and Distribution of Mucocutaneous Relapse Lesions. Where shall the conscientious physician examining his patient to detect



Fig. 420.—Apparently typical annular recurrences on the shaft of the penis. They are typical lesions of lichen planus, however and not of syphilis. There were lesions elsewhere, including the mouth. (See Fig. [illegible].)



Fig. 421.—The most disconcerting relapse in our experience. It came on in the midst of course of injections, after the patient had had four courses totalling 26 arsphenamine (606) injections, with no rest intervals and with alternating courses of injections. The blood Wassermann reaction was negative until the relapse occurred.

evidence of infectious relapse, direct his search? The sites on which mucocutaneous relapse lesions may be expected to appear are presented in Figs. 424–426 from the study by Stokes, Besancon and Schoch and in Fig. 427





Fig. 422.—Two successive relapses in the same patient following neglect of treatment. The first took the form of neurorecurrence ith hemiplegia. The second was a cutaneous relapse of an indurated papular type. Both occurred within the first eighteen months. Reinfection excluded.



Fig. 423.—This patient infection was of nine months duration. When his chancre was one week old he had received single dose of neoarsphenamine, and the lesion disappeared. Nothing further was done

Three months later the throat swelled and became so sore he could not eat. The physician, apparently not recognizing the condition, treated it locally for several weeks, and then gave him 3 injections of neoarsphenamine following which his throat cleared up.

Another four months now passed without incident. Then red spots and lumps developed on his arms, legs, and scalp These became crusted ulcers and the enormous gumma shown above developed over the tibia.

This patient result of inadequat treatment had advanced as far in the course of his infection in nine months he might be expected to in nine years. His condition had become so refractory that t was only ith difficulty that response could be secured with arsphenamine and mercury This patient as seen before the days of bismuth

Th blood Wassermann re ction was repeatedly negative.

Several types of relapse lesion are likely to be present in any given case. Sixty-one per cent of the relapse lesions observed by us were infectious, or

Fig. 424.

LESIONS PRESENT IN EARLY SYPHILITIC CUTANEOUS AND MUCOUS MEMBRANE RELAPSE (56 CASES)

1. Mucous patches	19
2. Dry papules in erodable sites	11
3. Papular lesions, generalized	11
4. Moist papules	11
5. Dry lesions of all kinds, trunk, face, extremities	11
6. Annular lesions	9
7. Monorecidives (recurrent chancres)	7
8. Condylomas	6
9. Chancriform papules	6
10. Macular lesions	3
11. Delayed secondaries	2
12. Follicular lesions	1
13. Pustular lesions	1
14. Alopecia	0

From Stokes, Beerman and Schoch, Jour. Amer. Med. Assoc., January 31, 1931.

potentially so, and 90 per cent of the 60 relapses presented infectious lesions as part of the relapse. (Seventy five per cent of Kern's (1941) relapse cases

Fig. 425

GENERAL LOCALIZATION OF RELAPSE LESIONS (56 CASES)

Anus and genitalia only	23
Generalized	13
[illegible]	10
[illegible]	5
[illegible]	4
[illegible]	1

From Stokes, Beerman and Schoch, Jour. Amer. Med. Assoc., January 31, 1931.

were darkfield positive.) No figures better emphasize the importance to public health of early relapse from the standpoint of potential transmission of the

Fig. 426.

LOCALIZATION OF ANOGENITAL LESIONS OF RELAPSE

Penis	26
Scrotum	11
Perianal	4
Vulva or labia	4

From Stokes, Beerman and Schoch, Jour. Amer. Med. Assoc., January 31, 1931.

disease. It should be borne in mind that these high figures were not the result of case selection but represent the typical situation in practice. Morphologically speaking, the mucous patch is the most important relapse lesion numerically. Condylomas and moist papules combined form the second largest

category Dry papules in erodable sites were largely penile in location. Nearly half the annual lesions occurred on the genitalia and this *ipso facto* should render annular lesions on the genitalia open to suspicion. Monorecidives or recurrences of the chancre and chancriform papule formed 13 per cent of the infectious recurrences. The anogenital region is the exclusive site of relapse

Fig 427

REGIONAL DISTRIBUTION OF THE COMMONER RECURRENCES ON THE SKIN AND MUCOUS MEMBRANES

Scalp.—Recurrent moth-eaten alopecia. Papular and pustular or even rupial recurrences at the hair margin. Circinat and gyrat groups of small ulcers suggesting acne necrotica, but with a configuration and arrangement that can only be recognized on clipping the hair Psoriasiform syphilids resembling psoriasis and seborrheic dermatitis of the scalp.

Face.—Thinning of the eyebrows, usually outer third. Rosaceiform papular lesions of the nose Hypertrophic nodular lesions suggesting lupus vulgaris. Mottled chin, a maculopapular syphilid of the secondary type. Annular recurrences about the chin, cheeks, and forehead. Fissure at the nares.

Lips, Mouth, Tongue, Pharynx.—Mucous patches, especially on the lip, t the commissures, etc. (see "Summary of Infectious Lesions) Deeper erosions along the margin of the tongue Papular recurrences on the dorsum of the tongue often denuded of papillae but not eroded. Late recurrences suggesting unusually destructive mucous lesions, usually several in a group, with a suggestion of arciform configuration. Lingual fissure Diffuse pharyngitis. Laryngitis, both simple and erosive with lesions on cords and epiglottis and varying degrees of hoarseness and phonia.

Neck.—Leukoderma colli, a mottled or macular depigmentation on a background of hyperpigmentation. This is the "pigmentary syphilid." It may occur on back, thorax, abdomen, or arms. It may be associated with the macular trophic secondary syphilid. Visible adenopathy can sometimes be made out in the neck.

Thorax and Back.—Mucous patches, moist papules and small condylomas under the breasts and in the axillae. Macular papular follicular corymbose and rupial relapses and recurrences. Pustular recurrences unusual Grouped follicular (large) papules and their scars. Extensive circinat gyrate urticarial and erythema multiforme-like lesions. Psoriasiform annular and gyrat recurrences. Atrophic macular syphilid, leukoderma. Disseminate late nodular lesions.

Abdomen.—Same as thorax. In addition, pudendal alopecia (especially women) and moist lesions t the umbilicus and in the groins.

Anus and Genitalia.—Relapse or recurrence of the chancre Dorsal lymphangitis of the penis, pipe-stem. Mucous patches, erosions, moist papules. The papular annular and erosive scrotal recurrences on both anterior and posterior surfaces. "Dry papule of the penis. Condyloma latum, especially with macular and papular eruptions and recurrences. Psoriasiform recurrences. "Syphilitic herpes progenitalis.

Palms and Soles.—P pular psoriasiform recurrences. Papular varioliform recurrences. "Eczematoid syphilid with indurated border and atrophic center Annular syphilid of the palms. Hyperkeratotic papular syphilid (syphilis cornée) Arciform and gyrat papular configurations of the type of lat syphilids. Verrucous syphilid. Moist papules and condylomatous lesions between the toes.

Nails.—Syphilitic onychia and paronychia. Symmetric spade nails.

Extremities.—Papular recurrences, flexor surfaces of forearms and wrists. Grouped follicular recurrences, extensor surfaces of forearms. Psoriasiform recurrences papular annular and gyrate Occasionally pigmentary residua. Syphilitic erythema nodosum.

lesions in 41 per cent of patients, the mouth alone in 17 % and of the anogenital lesions, 75 per cent occur on the penis or vulva the ideal sites for dissemination of the disease. That a large proportion of initial infections may occur on the genitalia may conceivably mean that the tissues in the regions of primary inoculation carry an appreciably higher spirochetal population, much as does the skin in the case of staphylococci about a boil. It may point

conceivably to an elective localization of the organism in this region of the body quite as much as to the effect of external conditions such as moisture dirt, and friction commonly accepted as chiefly influential in relapse by earlier observers. Half the lesions in the Pennsylvania series were infectious at the time of first observation Physical examination with special emphasis on inspection of the lip, penis, scrotum, and vulva, and not the blood serologic reaction is, therefore the chief method for the detection of infectiousness.

Darkfield and Serological Findings in Mucocutaneous Relapse.—*Spirochaeta pallida* is found by darkfield examination in mucocutaneous relapse with approximately the same frequency as it is in early primary syphilis, namely from 70 to 80 per cent of lesions (75 per cent

Fig. 428.

DARKFIELD DIAGNOSIS OF A MUCOUS RECURRENCE EIGHT DAYS AFTER THE HEALING OF AN ABORTED PRIMARY LESION

Young woman whose husband exposed her to infection while he was in florid secondaries.
Noted lesion on right labium minus.
Told by physician that husband had syphilis.
No darkfield, no Wassermann.
Physician gave her 2 intramuscular injections of what seems to have been soluble mercurial salt.
Patient left for Rochester at once.
Indurated Papule Left Labium Involuting on Arrival.
Darkfield Negative 3 examinations day for six days.
Wassermann every other day negative.
Primary lesion healed by seventh day Depressed scar
Eight days later although still Wassermann negative, patient reported new lesion on the labium.
Darkfield Positive. Many typical *Spirochete pallida*.
The lesion was some distance from the healed primary and was apparently either monorecidive or mucous patch.
Treatment Was Begun at Once.

DISCUSSION

1. Granted that the physician in charge of this case did not have the co-operation from the patient that he should, he was none the less culpable in that he had not sterilized the husband with arsphenamin at once when he knew him to be infected and infectious

2. He began treatment of the wife without an adequate diagnosis. No darkfield examination.

3. His treatment was ineffective. In such cases arsphenamin must be begun at once, and bismuth in whatever form should follow it.

4. Was the husband the source of the wife infection? Not necessarily The woman primary lesion may have been merely an indurated recurrence of latent infection (previous marriage or other exposure) The promptness with which new mucous lesion followed the supposed primary suggests this. The negative Wassermann is somewhat against it. A latent infection producing recurrences might be Wassermann negative or be reversed to negative by the amount of treatment this patient received. The husband is, therefore, probably the source of the wife infection.

of Kern cases). In the Pennsylvania series the blood serological reactions were positive in 86.8 per cent; in the Cooperative Clinical Group series in 81 per cent. In spite of this high proportion of positive serological reactions emphasis should be placed on seronegative relapse as something which definitely can occur (see Fig. 428). Pautrier, in 1930, cited twelve authors who had reported on seronegative, darkfield-negative cutaneous and mucosal relapse, and adds 1 case of the same type as a genuine rarity from his own experience. The seronegative monorecidive has been reported by Hudelo and Rabut, who in a series of 54 monorecidives, found 21 to be seronegative. In our 7 cases in the Pennsylvania series, 1 was seronegative but positive to darkfield examination, and 4 of 7 monorecidives were darkfield positive.

The Relapsing Type of Secondary Syphilis—Delayed Secondaries.—The question as to whether there exists a definite relapsing type of early

syphilis, so far as mucocutaneous lesions are concerned can probably be answered in the affirmative The patient who is prone to develop relapse lesions may exhibit recurrent secondaries appearing from one to two years after the primary lesion (Fig. 430) with or without treatment in the early secondary stage, *cf* Pariser (1939) This group was distinctly recognizable in the Cooperative Clinical investigation and included 121 patients who had developed recurrent secondary lesions after the first year of the disease. Of



Fig. 430

COMPLETE CUTANEOUS RECURRENCE WITH NEURORECURRENCE FOLLOWING INEFFICIENT TREATMENT

Primary February 1920.
Diagnosed by inspection.
No Wassermann
Secondaries four weeks later
2 arsphenamin injections intramuscularly
12 gray oil injections.
Secondaries disappeared
Treatment discontinued.
Four months later secondaries reappeared.
Genital lesion also reappeared.

Patient had then been married two months.
He also developed iritis.
H entered the clinic nearly blind with neuroretinitis.
10/13/20 SWR +++
CSF WR neg., Nonne pos cells 23.
This patient has complet recurrence, including serious involvement of the eye and the nervous system, as result of insufficient treatment.

this number 17 per cent had had a previous crop of secondaries which had failed to confer immunity These patients likewise exhibited an increased tendency to serological relapse, amounting to 20 per cent as compared with 12 per cent in seronegative primary syphilis.

In practice every patient who has passed through the normal secondary incubation period of six weeks to two months since the appearance of his primary lesion without showing any signs of secondary eruption deserves watching from the standpoint *of a possible delayed secondary* and chronic

relapsing type Particularly if he is a user of alcohol, in our experience he may prove to be an inveterate recidivist, developing showers of infectious lesions without warning over a period of a number of years, and this in spite of what appears to be thoroughgoing treatment

Fig. 430

RELAPSING TYPES

COMPLETE CUTANEOUS RECURRENCE AFTER TWO AND A HALF YEARS IN A CASE SEEN AS SWR BECAME POSITIVE IN PRIMARY STAGE

Penile lesion SWR neg., 11/17/16.
12/8/16 SWR ///
6 injections arsphenamin.
6 Hg. salicylate same time.
1/17/17 SWR neg.
4 Hg salicylate.
2/[illegible]/17 SWR neg.
16 Hg. salicylate.
8/16/17 SWR neg.
10/[illegible]/17 SWR neg.
4 injections arsphenamin.
16 Hg. succinimid.

Disappeared after 16 injections arsphenamin and 36 Hg. salicylat and 16 Hg. succinimid injections in eleven months.
SWR neg.
Returned two and half years later with complete cutaneous recurrence. Secondary papules on palms and soles, papules on penis.
No evidence of reinfection.
SWR ///
CSF negative.

1 This patient, observed carefully for four more years, has shown no further tendency to relapse following 12 more injections of arsphenamin, [illegible] additional injections, 23 Hg. succinimid injections, and 317 gm. sodium iodid intravenously
2. This was a typical example of repressed secondaries.



Fig 431 —A corymbose papular relapse after 14 injections of neoarsphenamine, without mercury The original secondary eruption was macular The patient husband had also had macular eruption, diagnosed "heat rash, and finally recognized as syphilid when he insisted on having blood test, after hearing public lecture by health officer on the subject of venereal disease.

The Transition from Recurrent to Late Syphilids.—The earlier in the course of a syphilitic infection a relapse occurs, the more closely the lesions

correspond to those of the secondary period, both in individual characteristics and in their wide distribution. With the passage of time in the course of the disease these recurrences tend to assume more and more the characteristics of late syphilids in that they are fewer in number and more destructive in character. Thus one sees extraordinary combinations in relapse including showers of nodular infiltrative and destructive lesions widely distributed over the body and even involving the mucous membranes, each individual lesion or group of lesions having distinctly gummatous and late syphilitic characteristics. Recurrences of this type were accepted parts of the course of



FIG. 432.—THERAPEUTICALLY RESISTANT SYPHILIS.

This patient presented a seronegative darkfield positive penile chancre, January 23, 1931. On February 20, 1931, after 6 injections of arsphenamine (606), total of 2.3 Gm., the penile lesion was still present and the BWR negative.

The arsphenamine was continued at weekly intervals, and on March 13, 1931, it was noted that the patient had developed several psoriasiform papules on the right leg which were darkfield positive. These lesions resisted treatment with neoarsphenamine twice weekly until April 13, 1931, when the patient was placed on intramuscular injections of boiled milk with subsequent rapid involution of the lesions.

Total treatment from January 23, 1931, to April 13, 1931, consisted of 9 injections "606," total of 3.5 Gm., 4 injections of tartroquiniobine, total of 8 cc., and 4 neoarsphenamine injections, total of 2.4 Gm. The blood serological tests were always negative. Patient was continued on combined therapy until May 29, 1931, when he was lost sight of.

a syphilitic infection in the old mercurial days and it is only the comparatively symptomless course of the disease under modern treatment which makes them objects of astonishment and admiration for us. In Figs. 416, 421, 433, 434 lesions of this type are illustrated.

The so-called neurosyphilid of Unna, or circinate roseola, is a comparatively rare lesion which for the most part appears as a recurrence, often years after initial infection, and even at times in association with late nodulo-ulcerative syphilids. This type of roseola is usually situated upon the trunk or extremities in the form of distinct or imperfect erythematous or erythematopapular rings, at times concentric with a tendency toward gyrate configuration. Combes (1930) reported a case and reviewed the literature. Hall and Schaerrer (1934) observed the neurosyphilid

of Unna in patient with congenital syphilis and considered it as an abortive type of late granulomatous cutaneous syphilis.

Effect of Inadequate Treatment on Recurrences—Precocious Tertiarism. —It is essential to recall that the chronology of syphilis with respect to early and late manifestations, can be sharply disturbed by improperly conducted treatment. The allergy or "*Umstimmung*" induced by inadequate treatment, especially with the trivalent arsenicals, has been discussed from the immunological standpoint in Chapter I. *Its clinical manifestations are illustrated in* such lesions as that of Fig 423 in which the patient is advanced to the stage of late gummatous and highly destructive manifestations profoundly resistant

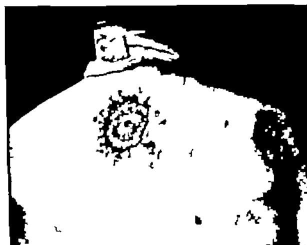


Fig 439.—An example of the type of recurrence which assumes late destructive characteristics as result of the allergy that follows inadequate treatment. The lesions approach the corymbose type.

The patient stated that she had default primary lesion, and that when her secondary eruption appeared in May 1919 her physician had given her one injection of arsphenamine and told her that nothing further would be necessary because one dose would cure.

Her first cutaneous relapse occurred six months later in the form of disseminated eruption. The Wassermann reaction on the blood being positive, she received second arsphenamine injection, and the eruption disappeared.

Her second recurrence followed, year later as shown bove. There were ulcerative lesions of late type in the larynx in addition to the skin lesions. The blood Wassermann reaction was positive, the spinal fluid negative. She had not at any time received mercury That she was not arsenic fast was evidenced by prompt response to intensive treatment.

The blood Wassermann reaction in such patients may be negative.

to treatment, through the simple but disconcerting intermediation of an insufficient amount of an arsenical Aside from the fact that the arsenicals in sufficient amounts are chief effective agents for the control of infectiousness, the risk of inducing precocious tertiarism furnishes of itself an additional reason why arsenical treatment in early syphilis should always be adequate.

Causes and Prevention of Infectious Relapse.—The causes and prevention of mucocutaneous recurrence are discussed in connection with the treatment of early syphilis. (See also Fig 438.)

Serological Relapse —*In the subsequent chapter on the treatment of* early syphilis serological relapse is dealt with incidentally to the consideration

of the serological effects of treatment, but the following brief summary orients the subject for the relapse problem in general. Serological relapse, by which is meant the recurrence of a positive blood serological reaction following suspension of treatment in a patient who had become seronegative, occurs with approximately the same frequency as mucocutaneous relapse (15 1 per cent) Its frequency of occurrence as influenced by the time at which treatment for syphilis is begun, is in interesting contrast to the course pursued by mucocutaneous relapse While mucocutaneous relapse decreases in frequency when treatment is begun after the seropositive primary stage, serological relapse increases slightly in frequency the later treatment is begun In this particular serological relapse then parallels the behavior of neurosyphilis and cardiovascular syphilis, both of which are but little affected or slightly decreased in frequency when treatment is begun in the seronegative primary instead of the secondary stage There is a close correlation between



Fig. 434 —Cutaneous recurrence within year after 9 neoarsphenamine injections The patient syphilis had been identified in Wassermann follow up, apparently for he had had no recognizable chancre or secondaries, though another man exposed under the same circumstances at the same time developed typical infection.

the behavior of the serological reaction and the occurrence of clinical forms of relapse Moore and Kemp showed that the patient who underwent serological reversal very early in the course of treatment for his infection had a demonstrably low resistance to the disease and a tendency to serological relapse. On the other hand, persistent refusal of the serological reaction to reverse under effective treatment is a warning of a relapsing tendency In patients who become serologically negative in the first year of treatment, the likelihood of relapse is represented by 10 1 per cent, as contrasted with 33 per cent in those who require longer than a year to become serologically negative or who become Wassermann fast. Serological resistiveness is, moreover a definite warning of early relapse of the secondary type, either mucocutaneous or ocular in character for there were 25.5 per cent of such relapses among 1292 patients of the Cooperative Clinical Group who were serologically resistant, as compared with 5 per cent of 1902 patients with a more satisfactory

Wassermann response. This same difference is apparent, though much less marked, for central nervous system relapse, which occurred in 30.6 per cent of patients with markedly delayed serological reversal as compared with 18.3 per cent of those who had a more favorable course. A similar tendency is apparent in other forms of late syphilis (2 per cent as compared with 0.7 per cent). Taken in the aggregate the total relapses of patients always seronegative or reversed to negative within the first year was only 22.5 per cent as compared with 48.1 per cent in patients whose serological tests showed delayed reversal. The importance from the standpoint of treatment and cure of the weak positive serological test appearing in a series of negatives during the treatment of early syphilis is presented on page 672.

Relapse Lesions in Bones.—The course of relapse as it affects bony structures is probably similar to that in the skin. The earlier lesions, while they produce local edema and inflammatory changes in the periosteum with swelling and points of exquisite tenderness, do not at first give rise to deposition of new bone with the production of permanent thickening. Similarly gummatous osteomyelitic processes do not appear until comparatively late except in cases undergoing the changes of precocious tertiarism.

A physician, age thirty-three, illustrated all the critical aspects of relapse causation and therapy. A chancre and secondaries, self-treated by successive irregular courses of sulpharsphenamine and casual mercurial treatment by mouth, was complicated by an agranulocytosis which he survived. Following this, wholesale necrosis and slough of the nasal and palatine bones appeared as a precocious tertiary type of relapse, controlled by boiled milk and bismuth injections, but relapsing and extending when treatment was stopped because of reactions (fever nitritoids). Malarial inoculation suggested, was deferred until a fulminating progression of the process had removed the entire interior of the nose, opened the accessory sinuses and involved the floor of the skull. Malaria when induced, had to be terminated because of a nearly fatal recurrence of the agranulocytosis. It had been carried far enough however so that recovery began and was continued, under mercurial inunctions, bismuth, intravenous iodide and conservative local treatment of the nasal cavity. A morphinism was nipped in the bud, and despite the extent of the internal destruction, the patient's appearance was but little changed. His spinal fluid was normal.

In all probability the comparative nonrecognition of bone recurrences is the result of the fact that the osseous system is largely covered by softer tissues and concealed both from the eye and other forms of observation. Lacking destructive character therefore, the early lesions largely escape detection, the symptomatic discomfort which they produce being lost in the general complex of rheumatoid symptoms associated with the early years of the disease. Bone and joint relapses have no particularly distinctive features and are sufficiently summarized in the general consideration of syphilis of the skeletal system (Chapter XVI).

Eye Lesions.—The commonest lesion of relapse or progression involving the eye is iritis, which is considered on page 604. Neurorecurrences involving the eye and particularly the second, third and fourth nerves, are identical with neurorecurrence in general and with the ocular symptoms of basilar meningitis as presented in Fig. 404 and in the chapter on neurosyphilis.

Birth of a Syphilitic Child as Relapse.—The problem presented by the syphilitic pregnant woman is considered in connection with the immunology of the disease (p. 31), the collateral factors of treatment (p. 447) and prenatal and familial syphilis (p. 1148). It should none the less be emphasized here that the situation presented in Fig. 435 is by no means an impossible or even

an excessively rare one. It is impossible absolutely to insure the noninfectiousness of a syphilitic mother with respect to her child and even thoroughgoing treatment before or during pregnancy is not an infallible protection. Figure 349 in Chapter XXI presents a child with a mild but incontestable prenatal syphilitic infection acquired from the mother while the mother herself was supposedly under adequate treatment with neoarsphenamine and bismuth

Warning →
Neurorecurrence
Wassermann relapse →
Syphilitic child →
Wassermann relapse →
Wassermann relapse →
Total 25 arsphenamine injections
245 – 30 gram mercury rubs
19 ½ mercury succinimide injections

Fig. 433.—Record protocol of the case described on page 643, illustrating the birth of syphilitic child as form of relapse, five years after infection followed by neurorecurrence in previously negative spinal fluid. Rise in cell count as warning of abnormality early in the disease.

Fig. 435 (Continued)

EXTRAGENITAL CHANCRE (LIP). MISDIAGNOSED BECAUSE OF EARLY NEGATIVE WASSERMANN SUBSEQUENT SECONDARIES WITH POSITIVE DARKFIELD AND POSITIVE WASSERMANN. SPINAL FLUID SLIGHTLY ABNORMAL TWO YEARS AFTER INFECTION. REDUCED TO NEGATIVE BY TREATMENT. GIVEN PERMISSION TO MARRY AFTER THREE YEARS. FIRST CHILD HEREDOSYPHILITIC. SUBSEQUENT TOTAL RELAPSE IN NERVOUS SYSTEM AND BLOOD AFTER FULL COURSE OF TREATMENT

Woman, aged twenty-six, examined 10/2/16.

Chief Complaint: Gland in neck and sore lip. T months duration. Sexual exposure admitted. No kissing within one month.

Examination Indurated, crusted, partly healed ulcer left lower lip. Swollen submaxillary node. Blood Wassermann reaction negative. Consultant advice "Has had some kind of medication internally Wait t weeks and repeat Wassermann. No darkfield taken.

Re-examination 9/10/17 returns with the chief complaint of epigastric pain and vomiting. Sharp hunger pains. Ulcer on lip replaced by large mucous patches. Gland still present. Darkfield showed *Spirocheta pallida*. Blood Wassermann reaction positive.

This patient summarizes all of the problems and difficulties presented by the diagnosis and treatment of early syphilis t the present day as follow

1 Her primary lesion on the lip was not diagnosed because of overdependence on the negative blood Wassermann examination and failure to make darkfield examination.

2. She was permitted to go on to mucous membrane secondaries, the blood Wassermann becoming positive but no secondary eruption developing on the skin.

3. In conjunction with her secondary manifestations she exhibited probable acute syphilitic gastritis which cleared up under treatment.

4. When her condition was finally recognized by darkfield and blood Wassermann in the fully developed secondary period, she was placed on what might properly be regarded as intensive modern treatment. The first two courses ere given with sufficient dosage, proper intervals, and proper interim mercurialization. The patient then broke treatment for several months.

5. Spinal fluid examinations were not routine part of the treatment of early syphilis in this department until 1918. Accordingly no examination of the spinal fluid was made until after the second course of treatment.

6. The fluctuating blood W ssermann reaction, however strongly positive once during the second course of treatment, warned us that this infection was not completely under control. A spinal fluid examination tw and half years after infection showed negative Wassermann and globulin, but *pleocytosis of 11 cells*. At that time we were just beginning to realize that even very slight rise of cell count, while not significant in itself in patient ith early syphilis may be warning of involvement of the nervous system and the precursor of serious neurorecurrence.

7 The patient therefore consented to resume treatment, and 9 more arsphenamin injections reduced the spinal fluid almost t normal. A weak positive blood W ssermann reaction, however gain roused us that the disease was not completely extinguished, and still more treatment as given.

8. The patient was not given permission to marry until four and half years after infection, when her spinal fluid was completely negative nd her blood Wassermann reaction had been negative continuously for one year (five tests).

9 In spite of these precautions she gave birth to heredosyphilitic child more than five years after her infection, and one year and six months after all clinical and serologic signs of the disease had disappeared.

10 Her blood Wassermann reaction as negative during her pregnancy

11. The test became eakly positi three months after the birth of the child, and was negative twice during the following fourteen months, but she did not pursue treatment.

12. Her asymptomatic neurorecurrence was heralded by weakly positive blood Wassermann which subsequently became strongly positive. A more or less routine examination of the spinal fluid was the only thing hich detected the final serious involvement of her nervous system seven years after the onset of her infection.

DELAYED NEURORECURRENCE WITH OUTLY NORMAL SPINAL FLUID

	Date	Blood Wassermann reaction	Cerebrospinal Fluid: Wassermann 0.4 cc	0.6 cc	1.0 cc	Nonne	Cells	Colloidal gold test	Remarks
8 arsphenamine injections.	1/1/'20	++++							Chancre involuted rapidly
	11/8/'20		—		—	+	1		
20 inunctions	11/9/'20	++++							
	11/27/'20		—		—	—	2		Completed course 1; no complaints.
40 inunctions	1/13/'21	—							
6 arsphenamine injections	1/25/'21		—		—	+	6		Notice cell count.
	2/17/'21	—							
20 inunctions 40 inunctions									Completed course 2; feels fine.
	4/14/'21	—							
6 arsphenamine injections	4/23/'21		—		—	—	10		Watch cell count.
									Completed course 3; no symptoms.
40 inunctions	7/7/'21	—							
6 arsphenamine injections	7/16/'21		—		—	—	14	0000000000	Further increase in cell count.
	8/10/'21	—							
20 inunctions									Completed course 4; no signs or symptoms.
	11/12/'21	++++							
	11/18/'21		++++		++++	+	33	5543321000	Recurrence; no signs or symptoms.
2130 c.c. NaI, intravenously 1 mercury succinimid 8 arsphenamine								—	Acute hyperthyroidism on adenoma; thyroidectomy.
	2/13/'22		—	—	—	—	10	5554310000	
	4/[illegible]/'22		—	—	—	—	1		
	5/20/'22		—	—	—	—	1	0000000000	Overtreatment syndrome.
2 intraspinal 40 inunctions	/20/'22	—							
	10/ '22	—							
	10/14/'22		—	—	—	+	2		
	1/[illegible]/'23	—							
	2/[illegible]/'23	—	—			—	1		Epidemic encephalitis? death 2/[illegible]/'23.
	2/20/'23		—	(Kolmer technic)		+	2	Sugar 18%	
	2/20/'23		—			+		Culture; no growth.	

Fig. 436.—Spinal fluid record of   patient seen in the primary stage, normal at the outset, with   neurorecurrence (asymptomatic) after repeatedly normal fluid findings. Warning of relapse in the form of slight rise in cell count. Controlled by sodium iodide and mercury succinimide, but the use of the iodide produced toxic symptoms in   thyroid adenoma, and thyroidectomy was necessary. Death later from encephalitis (lethargic or syphilitic?) No spirochetes found in any tissue.

The general bearings of this question are given on page 1115 (prenatal syphilis chapter)

REINFECTION

Frequency of Reinfection.—*Reinfection is a comparatively rare event* in the course of syphilis today In the University of Pennsylvania series, reinfection occurred not oftener than 4 times in 2439 cases, or once in 609 cases. White reported 1 in 375 cases Driver 1 in 384 cases Cederkreutz, 1 in 1580, and Bernard, 1 in 600 Reinfection occurred in our series once in 228 cases, in comparison with the frequency of primary and secondary syphilis. Moore and Kemp gave a frequency of approximately 1 in 131 cases of primary and secondary syphilis. From the practical standpoint *it is difficult to imagine* that the incidence of subsequent exposure of persons with syphilis to risk of reinfection falls to as low a figure as 1 in 710 cases, which is the average of the foregoing figures for frequency of reinfection exclusive of those involving only early syphilis. It therefore follows that few exposed persons are reinfected and if reinfection is a criterion of cure, few indeed are cured. So-called "pseudo-reinfection" has been particularly discussed by Belzer Hecht Bernard, Lortat-Jacob Roberti, and Pouneau-Delille.

The Clinical Characteristics of Reinfection.—In Chapter V in discussing reinfection as an evidence of cure the various criteria established by the most extended surveys of this topic were outlined (Fig. 73) It is worth recalling that no reported reinfection up to the date of the review of the subject by Stokes, Schoch, and Ireland, and the Cooperative Clinical Group, had qualified for acceptance under the most stringent code. The reporting of a *valid reinfection is one of the most difficult accomplishments in the syphilological field*, and the larger part of the evidence now in existence for individual cases must rank as presumptive or suggestive rather than conclusive. A very large part of reinfection unquestionably resolves itself into relapse, and a proportion of it into the probable but not yet fully established entity of superinfection. The reports of reinfections in patients treated by intensive systems of therapy have been discussed on page 185

There *is a tendency to dismiss as largely of historic value the clinical* criteria for differentiation between the lesions in a relapse and those of an alleged reinfection (Bernard)

Hudelo and Rabut (1924) viewed the matter more as we believe it must be viewed in this country today that the "explosion of reinfections in the months following the use of '606' and '914 must be viewed as false reinfections—chancriform recidives dependent upon colonies of spirochetes isolated from the circulation by tissue reactions." The same is undoubtedly true for intensive therapy (See Chapter XIV) The negativity of the Wassermann reaction of the blood in such cases has only a relative value, for "it is frequent in the course of secondary relapses." We are therefore compelled to regard as insufficiently critical the second of the two criteria of reinfection accepted as adequate by Halley and Wasserman "After an interval following antisyphilitic treatment and at a site other than that of the primary lesion of the first infection, there must develop a lesion with the characteristics of a chancre in which the spirochetes can be demonstrated." We believe that such lesions occur also in definite categories of relapse.

The monorecidive has already been described as one of the common forms of relapse. Critically speaking, the criterion for differentiating the

chancre of an alleged reinfection, from a mere monorecidive, then, should be an interval of at least a year and preferably two years between the first and second infections (85 per cent of monorecidives fall in the first two years of a syphilitic infection which is identical of course with the general period of relapse) The site should not be identical in the two infections, and should not even be in the same lymphatic drainage. Hecht, however pointed out how little the lymphatic drainage of the genitalia, with its rich anastomoses, may mean for such a criterion In our opinion, the case illustrated in Fig. 437 is an example of the puzzling question of regional distribution of possible relapse foci about the scar of a chancre. The monorecidive like the chancre, should be darkfield-positive, but the organisms, as emphasized by Hell, are *fewer than in the original active chancre, a criterion rendered somewhat* unreliable, however by the relation known to exist between the number of organisms and the age of any primary lesion The chancre in reinfection is



Fig 437 —See case history Fig. 405. The induration in the old scar is visible at A; the lesion from which spirochetes were obtained is posterior at B.

supposed to be seronegative at the onset and later to become seropositive, while the monorecidive, being part of a recurrence, is supposed to be more frequently seropositive at first recognition Hudelo and Rabut, however found 21 seronegative monorecidives in their series of 54 Our experience with relapse in general however indicates that it tends strongly to be seropositive at the onset and that the demonstration that the blood serologic reaction is positive in a supposed reinfection less than a week old is strong evidence in favor of relapse. Occurrence in or close to the site of the original primary lesion within a year of the original infection of a lesion seropositive on first sight, is the strongest evidence albeit subject to exception, for the *identification of a monorecidive The demonstration of Spirochaeta pallida,* or their relative number does not infallibly serve to distinguish the monorecidive from a *bona fide* new chancre.

The chancriform papule an easy source of confusion with the chancre

of a supposed second infection, is a large, solitary papular recurrence in the secondary stage of the disease Its occurrence about the genitalia, where it may become eroded and swarm with *Spirochaeta pallida*, provides the characteristics for confusion. It is a curious fact that of the supposed reinfections we have observed, the best authenticated cases from the standpoint of general criteria have had lesions at least suggestive of typical Hunterian chancres to mark the onset of the second infection. On the other hand among 54 undoubted lesions of relapse studied by Stokes, Besancon and Schoch, they observed 6 typical chancriform lesions as part of relapsing secondary eruptions. Hudelo and Rabut observed 13 examples of isolated chancriform papules on the penis among the 54 monorecidives which they studied.

Figure 437 is an illustration of the difficulty in differentiating apparent reinfections from the standpoint of history from the morphological appearances of mucocutaneous relapse. A group of new primary lesions or chancriform papules may develop about the site of a primary scar sometimes with and sometimes without induration of the scar The difficulty of differentiating such lesions from secondary recurrences is obvious. Hashimoto has reported that in some of his experiments on superinfection multiple small papulo-erosive lesions without the production of a typical secondary chancre are observed. Hecht has pointed out that a similar arrangement about the scar of a chancre can be a feature of secondary recurrence, and he has suggested, furthermore, that the site of the original chancre may be specially susceptible to reinoculation on further exposure.

It must be apparent, then, that exceptional difficulties confront any observer who desires to report an "air-tight" case of reinfection, for the confusion borderline between relapse and the experimental shadowground of superinfection is still too full of uncertainties for absolutely safe pronouncements. In view of the uncertainties attaching to the terminology more and more observers are giving up the use of the term "reinfection" and substituting "second infection" for it.

Progression and Treatment-fastness in Early Syphilis.—When the patient under treatment proceeds to develop or continues to develop lesions of whatever structure the condition is spoken of as progression Obviously treatment-fastness and progression are closely related. Under the heading of drug resistance, various aspects of treatment-fastness have been discussed on pages 146 to 149 Figure 432 is an excellent illustration of treatment fastness in the form of progression of cutaneous lesions in the course of active treatment. The graver forms of progression, however are those which involve particularly the cardiovascular and the nervous systems, and these differ from the manifestations of progression in other structures in that they are comparatively much less influenced both by the mass and the method of treatment. There is about them, and particularly about cardiovascular syphilis, a certain inevitability which emphasizes the fundamental uncertainty of all statements regarding "cure." The material of the Cooperative Clinical Group covering the period from 1910 to 1930 indicated that progression in neurosyphilis, in spite of good arsphenamine and heavy-metal treatment, occurs in approximately 6 to 7 per cent of patients under a time-treatment method of appraisal. Progression of cardiovascular syphilis under similar conditions occurs in 0.8 to 1 1 per cent of cases. Progression under treatment is controllable to some extent by the mass and prolongation of treatment. Even the most thoroughgoing treatment, however does not protect neces-

sarily against the development of abnormalities in the spinal fluid (asymptomatic neurosyphilis) Much treatment prior to the development of the abnormality had been given in 45 6 per cent of 101 cases which subsequently developed abnormal spinal fluids in spite of treatment. The inevitability of cardiovascular involvement in a certain proportion of cases in spite of thoroughgoing treatment, is indicated even more strikingly by the figures 0.9 per cent progression with little treatment and 1.2 per cent with much treat

Fig. 438.

THE PREVENTION AND TREATMENT OF RELAPSE AND PROGRESSION

1 Expect relapse in 5 t 15 per cent of the run of clinic patient with early syphilis (treated by all methods including modern intensive arsenotherapy).
2. Try to forestall and recognize it by:
 (a) Frequent serological tests, taking weak positives seriously
 (b) Thorough, frequent examination of the mucocutaneous surfaces, especially of the mouth, anus and genitalia, palms and soles, within the first two years after treatment is stopped.
 (c) Instruction of the patient as t occurrence and signs.
 (d) Especial vigilance in patients who develop lat or delayed secondary manifestations.
 (e) Especial vigilance in patients whose blood serological reactions reverse t negative immediately after treatment is started.
 (f) Being on guard, especially for explosions of delayed or suppressed secondaries in patients who began treatment as seropositive primary cases or who have been inadequately treated in that stage.
3. Insist on spinal fluid examinations, with one repetition after an initial negative (7.5 per cent may show progression even in spite of treatment)
4 Prolonged treatment
 (a) With the arsenicals beyond the t entieth injection and as near t 40 injections as possible or by an effective intensive foreshortened method.
 (b) With the heavy metals, until at least one year after all signs disappear
 (c) For two years or more beyond the last sign if relapse has once definitely ppeared.
5 Make treatment continuous, not intermittent, "intensive or irregular
6 Vary the drugs used if signs of resistiveness ppear such as:
 ( ) Persistence of spirochetes or lesions beyond a "normal" period.
 (b) Recurring weak positive blood tests in series of negatives.
 ( ) Outright signs of relapse.
7 Turn to "606" if "914 has failed, or use it from the start.
8. Trust arsphenamine-bismuth more than arsphenamine-mercury combinations. But mercury inunctions and intravenous odide may occasionally succeed when As and Bi fail.
9 Employ nonspecific methods early if others fail. Nonspecific protein, malaria, fever chemotherapy are all effective if persisted in.
10. Interdict alcohol. The periodic drinker is an almost inveterat relapser
11 Utilize iodide and the rest period in late recurrences (see Serologic Fastness).
12. Mak no promises bout pregnancy

ment. All other forms of progression however are fortunately considerably more marked under insufficient than under much treatment.

At the risk both of tedious repetition and the forestalling of unconsidered material Fig 438 epitomizes briefly the general principles of prevention of relapse and progression.

It will be seen, then that the control of relapse lies less in the treatment of consequences than in the thoroughgoing attack on the infection at the outset. It is essentially preventive rather than curative No variety of drugs or methods used late can take the place of a powerful arsenical an l bismuth

therapy at the outset, very short or no rest intervals from treatment as a whole repeated courses intelligent reinforcement of the resistance mechanism with mercury bismuth and nonspecific measures complete serological and clinical control—in short, all those things which make up the rationale of effective treatment so far as we know it today The resistant infection and persistent relapser will tax the consultant's ingenuity to the utmost. The patient whose tendency to relapse resists all these measures must bow as to the inevitable. He must wear his infection out or be conquered by it.

CHAPTER XIV

THE TREATMENT OF EARLY, EARLY LATENT AND LATE LATENT SYPHILIS*

Perhaps the best approach to the modern treatment of early syphilis (and this includes early latency and even later latency) is a series of short sharp categorical and hence to some extent disputable statements indicating land marks in the progress of the past thirty-five years. Such a summary is substituted for a narrative type of historical perspective in the present edition of this work. The personalities and the play of thought dominate the summary in the second edition. Reference may be had to it by those desiring such a presentation.

The Mercurial Era.—Syphilis therapy up to 1912, it becomes increasingly apparent, left the disease syphilis to pursue its physiopathologic course comparatively little influenced at least by the milder and hence most popular forms of medication—the therapy *per os* of the widely copied French school. Even mercury intramuscularly except as the water soluble salts, and the violently reaction-producing calomel veneered the surface of a syphilitic infection, rather than attacked its roots.

The Early Arsphenamine Era.—The "therapia sterilisans" period or one-dose cure era promised by Ehrlich's theorization slowly changed under the impact of criticism from older observers of the course of syphilis under treatment. Belief that something radical, timesaving and treatment-shortening had been accomplished by 606 died hard. One dose was succeeded by successive doses as experience grew. Relatively new conceptions of "cure by stage" came into existence with curious incomprehensible off-shoots such as the doctrine of chancre-excision. "Abortive cure" essentially the systematic speculative under-estimation of the amount of treatment required by the seronegative primary stage, dates back to this era. From 1916 to 1919 the "course" conceptions of syphilis treatment established themselves together with a combined theoretical and speculative discussion of the necessity for and the appropriate use of arsphenamine and heavy metal.

The Early Evaluative Period.—From 1919 to 1922 an extensive literature unfortunately not too familiar to some claimants for priorities, constituted the initial "shake-down" of an accumulating experiential tradition. While limited to the serologic effects of treatment and the occurrence of grossly visible forms of relapse as criteria for determining effects, many of the out lines along which the new era has developed were foreshadowed in the reports of Gennerich, the German Dermatological Society (Rost 1921), Almkvist, Bering, Boas, Hoffmann, Bruck, Jadassohn, Ullmann, Hofmann-Mergelsberg, Müllern Aspegren, Haxthausen Rasch, Scholtz-Silberstein, Sathe, Mutschler, Zieler, Bruns-Riecke, Bernard, and Colonel Harrison. The stage-of-beginning-treatment conception received quite precise delineation towards the latter part of 1922. A type of foreshortened intensified therapy, that of Scholtz, was

* A bibliography for most of the material in this chapter will be found in review by Stokes, Beerman and Wammock, Am. J. Med. Sci., 206, 521, October 1943.

reported on by Silberstein in 1923, before any American contributions were in the field. When American contributions did appear however they rapidly established a series of *important conceptions, beginning with Moore and* Kemp's demonstration based on Keidel's foresighted Johns Hopkins system of the importance of continuity in treatment, and Becker's Mayo Clinic demonstration of the value of massing or intensification of arsenical therapy at the moment treatment is begun. Familiar to Americans during this period are the Pollitzer-Ormsby variation on the Scholtz intensive technic and other types of intermittent systems which lost ground after the League of Nations confirmation of the substantial superiority of continuous treatment.

The League of Nations Syphilis Commission Evaluations.*—Begun on a massive scale in 1928 with conclusions and recommendations stated in 1935 this world wide survey of technical methods in the treatment of early syphilis provides the basis for what may now be spoken of as the conservative or prolonged method for the treatment of early and latent syphilis. Under the terms of the cooperative agreement among the nations participating, each was individually encouraged to make the most of his own material in addition to contributing to the general pool. This rapidly brought American material into the foreground, and the contributions of the Cooperative Clinical Group† working under the aegis and with the statistical cooperation of the United States Public Health Service, express today what might be called the basic formula of American practice, referred to throughout this work as the USPHS-CCG data and material From the League of Nations evaluation for which Martenstein supervised the interpretations, two general systems of treating early syphilis emerged, the British-Scandinavian intermittent and the American continuous systems (see also Stokes and Usilton, 1937) A certain amount of argument has inevitably arisen over the suitability of the material for deciding the question of intermittence versus continuity but on the whole the Commission's findings seemed to justify the belief that the intermittence of the recommended intermittent system is more formal than actual and that its intensity especially in simultaneous arsenical and heavy metal administration, causes its effects to be substantially those of a somewhat less intensive but continuous technic. Enthusiasm for the newer foreshortened procedures should not be allowed to dim the significance of this great evaluative accomplishment, and the syphilologist of today may without hesitation subscribe to either of the announced conservative systems as the equal in curative effect of the more recent "hurry-up" systems of procedure with a substantially greater margin of safety

Since the League of Nations evaluation has established such substantial landmarks, it may well be used as a milestone at which to summarize the high-points of the progress of syphilotherapy since the close of the mercurial age.

* Under the direction of the League of Nations Health Organization, the following countries participated Denmark, France, Germany Great Britain, United States of America. The membership in 1928 included Jadassohn (Breslau) chairman, Madsen (Copenhagen), Colonel Harrison (London), Queyrat (Paris), Stokes (Philadelphia), Rasch (Copenhagen); Gougerot replaced Queyrat, Lomholt replaced Rasch in 1935. Statistical consultant, Westergaard (Copenhagen) Evaluation and report by Martenstein (Dresden).

† Cooperative Clinical Group composed of the heads of five syphilis clinics, Western Reserve University (H. N Cole), Johns Hopkins University (J. E. Moore), the Mayo Clinic (P A. O'Leary) the University of Pennsylvania (J H. Stokes) and the University of Michigan (U. J Wile), assisted by the United States Public Health Service (T Parran, J T Clark, R. A. Vonderlehr and L. J Usilton, statistician)

The following fundamental principles have emerged from a quarter century of revolutionary progress

1. Early and not late syphilis is the domain of systems. Bad effects follow haphazardness, short courses, low dosage and lapse from treatment in early syphilis.
2. The "stage-at-which-treatment-is-begun" principl is established with trustworthy evidence that seronegative primary syphilis is the most easily cured of all stages of the disease, seropositive primary syphilis the most uncertain or resistant and secondary syphilis midway between the two.
3. Relapse follows short treatment, especially arsenical.
   Delayed secondaries
   Neurorecurrence
   Infectious mucosal lesions
   Serologic relapse and fastness.
4. Single drug treatment is inferior to combined treatment, and heavy metal improves arsenical results and compensates shortcomings.
5. Prolongation—more injections, longer courses—gives superior results in systems dominated by the calendar interval of one week. Prolongation and increased mass through individual and total dosage were, of course, attempts to meet the resistance of the 20 per cent relapsing group among early syphilitics t large
6. Dosage theory was spotted with empiricism the concept of lower drug tolerance of the female as compared with the male the large *versus* small dose school; the crowding or time-dose problems represented by the so-called intensive method; the toxicity fears (simultaneous *versus* alternate administration of arsenical and heavy metal); the idiosyncrasy and technical error factors in reaction interpretation which held down dosage, while reports of relapse and resistance raised it.
7. Calendar servitude or the domination of the seven-day interval on a purely empirical unevaluated basis was general. Few ventured to think in terms of shorter intervals or would admit their practicality or desirability
8. Rising ppreciation of scheduling It became clear that schedules or systems critically examined by large syphilologic centers and expert experience were the sound basis for treatment methods rather than the results of blood serologic tests, thus slowly displacing the serologism of the 1920's.
9. Th vital comprehension of toxicity and therapeutic efficiency relations was dominated by the laboratory and rested on the insecure foundation of trypanosomiasis in mice rather than syphilis in man or animals. This group of conceptions, though expressed by impressive numerical indices, was essentially vague and inadequate. A true experimental basis for syphilotherapeusis did not yet exist.
10. Despite these strictures on the knowledge of the day the work of individual investigators plus the League of Nations evaluations established the following facts
    (*a*) An arsphenamine alon can cure" early syphilis in a large proportion of cases (Levaditi).
    (*b*) Heavy metal is potent ugmenting force, particularly true of bismuth; fact recently "rediscovered" by recent workers with intensive methods.
    ( ) Arsenical ther py can be crowded or "foreshortened" without fatal effect and ith good results (Scholtz-Silberstein massive divided dose system).
    (*d*) Continuity and calendar regularity are vitally important to the conservative or prolonged systems evaluated by the League of Nations. A little treatment continuously given is t ice as effective as the same amount of treatment intermittently given.
    ( ) Prolongation of treatment (in the weekly calendar or conservative systems) irons out most complications, relapse and resistance (except preparetic neurosyphilis).
    (*f*) Some important League of Nations and CCG principles the curative outlook is one-third better when treatment is begun in the seronegative primary stage than in other stages of early and latent syphilis; the good results obtained by prolonging continuous treatment for more than one year more than double those obtained by the same kind of treatment carried through less than year; intermittent and irregular treatment methods are the principal sources of delayed reversal of the blood serologic reaction; prolongation and intensification of treatment, using much arsphenamine and heavy metal, but especially much arsphenamine in the first three month promotes good results;

satisfactory results may occur with little treatment, but much treatment and over prolonged periods is twice as effective as little treatment if continuously applied, and five times as effective as treatment intermittently applied arsphenamine is the chief factor in relapse prevention, and this applies specifically t the incidence of neurosyphilis (note importance of this principle in foreshortened intensive methods). Serologic irreversibility becomes the more marked the later in early syphilis treatment is begun, and the more frequently lapse from continuity occurs whether in the form of rest intervals or otherwise weak positive serologic test interrupting series of negatives in early syphilis is distinct warning of the possibility of relapse.

Much of the effectiveness of the foreshortened intensive treatment methods was predicted by Martenstein conclusions from the general League of Nations material that the employment of comparatively heavy individual dosage of the arsenical and of bismuth or mercury with administration in rapid succession at the outset of treatment, leads to superior results. Furthermore, approximately the same amount of treatment should be administered to primary as to secondary cases.

(g) Large dosage is preferable to small; should follow weight standard, and be without sex differentiation.

(h) Many of the most serious complications of treatment are due to background causes (idiosyncratic-allergic, intercurrent infections, and technical factors rather than the drugs as such alone) In particular the combination of arsenic and bismuth is as safe as arsenic alone.

(i) Claims for the use of heavy metal alone in the treatment of early syphilis have not withstood critical evaluation. An arsenical is essential as controller of infectiousness. The effect is augmented by bismuth, and also, though probably less so, by mercury Twenty full doses each of arsenical and heavy metal approximate minimal amount of treatment for infection control (so-called 20-20 standard)

(j) The controversies over the individual merits of arsenicals (606, 914 and so forth) have been largely submerged by the overwhelming popularity of mapharsen in American practice, due largely to its low toxicity combined with high spirillicidal value. This has been overwhelmingly demonstrated in the five-day massive dose arsenotherapy (five-day drip), and its therapeutic efficacy when intensively employed has also been demonstrated by the Eagle-Hogan animal experiments.

ADDITIONAL BASIC PRINCIPLES FOR PRESENT AND FUTURE REEMPHASIS

1 The Boeck-Bruusgaard material underlies the principle that syphilis cures" itself in 40 per cent of cases.
2. A little treatment in early syphilis (Padget) raises the percentage of cure another 20 to 30 per cent.
3. Intensification and prolongation (or repetition in the case of intensive foreshortened methods) directed at the resistant 30 per cent bags another 15 to 25 per cent (depending on stage-of-beginning-treatment) for cure.
4. The remaining 5 per cent to 15 per cent represents the irreducible residue of resistance (deficient defense special strains and so forth) that nothing save time, therapeutic repetition and variation and fever if anything, will cure.
5. Nonspecific agents (fever) have important reenforcing and curative effects in early as well as late syphilis—chiefly by enhancing the effectiveness of arsenicals faster than it increases their toxicity (Carpenter Warren).
6. The spinal fluid examination is an indispensable evaluative and curative check procedure more important ultimately than blood serology
7 As to observation and discharge as cured, all patients who have had an entirely nonrelapsing course while receiving ideal treatment should be informed that cardiovascular reexamination in the five- to ten-year period is necessary
8. The syphilitic pregnant woman or the woman who has had syphilis and is believed to be cured, should have her status reviewed with every pregnancy and safety-first requires her treatment for protection of the child during each pregnancy whether seronegative or seropositive

9 Unsatisfactory results (noncure) are usually revealed by the fifth year of observation and Padget found no less satisfactory results in any case after ten or more years of observation.

PRINCIPLES ESTABLISHED BY THE CLINICAL AND EXPERIMENTAL STUDY OF FORESHORTENED INTENSIVE METHODS

The past decade of work with intensive treatment methods has contributed a number of additional important principles to our understanding of syphilotherapy

1 Hyman and his coworkers have demonstrated that an approximation to the total curative dose of an arsenical can be administered to a human being by an intravenous infusion method (drip) without necessarily disastrous effects with controllable though increased toxicity and with satisfactory therapeutic results.
2. A toxicity-therapeutic efficacy relationship has been worked out by Eagle and Hogan on the basis of animal, and more recently human clinical results. Syphilis can be cured in 80 per cent to 100 per cent of cases (stage-of-beginning factor) by a total dose of 20 to 30 mg per kilo body weight of an arsenoxide (mapharsen) alone.
3. The toxicity of such a dose is inversely proportional to the time in which this dose is given.
4 Any combination of toxicity and time relationship (that is, any margin of safety) that practical considerations may dictate is theoretically possible, the mortality rising with the shortening of the time in which the total dose is delivered.
5. The addition of bismuth ("rediscovery") greatly enhances the effect of all foreshortened intensive arsenotherapy (informally estimated by Eagle as 8 times better effect with bismuth than without)
6 Serologic signs and symptoms under foreshortened procedures disappear gradually on a now well-recognized gradient to which a quantitative serologic procedure is essential in interpretation.
7 A wide variety of time and technical variations (five-day intravenous drip *versus* ten-day multiple injection, *versus* ten to twelve weeks of two to three injections weekly *versus* twenty-six-week schedules with graded morbidity and mortality but substantially identical therapeutic outcome) can be employed as forms of "foreshortened intensive" systems in the name of various types of exigency or expediency
8. The mortality of the five-day drip is currently estimated at 1 : 200 to 1 : 300. Any schedule completed in twenty days or less will have a mortality greater than 1 : 1000 (Eagle-Hogan) ten to twelve week systems have a mortality of approximately 1 : 1500 The mortality of twenty and twenty-six-week systems is not yet definitely known. That of reasonably good performance of the standard conservative prolonged systems is estimated by Hahn (Johns Hopkins Hospital) at 1 : 1850 with optimum experience to 1 : 2800.

   It must be recalled that the mortality of conservative treatment is computed from arsphenamine and not mapharsen-treated cases. The toxicity of mapharsen is so low (one death in 3936 patients, Levin and Keddie 1942) that a material drop in mortality should follow its use in the conservative systems. Levin and Keddie estimate the mapharsen death-rate to be one-half that from neoarsphenamine
9 The foreshortened intensive procedures (up to twelve weeks) greatly reduce the incidence of neurosyphilis.
10 The justification of the foreshortened procedures except for their apparent efficacy in the prevention of neurosyphilis (spinal fluid abnormality) is in the main still one of emergency and expediency The ultimate results are obtainable by the older slower methods with less risk to life What effect this will have on their post war use remains to be seen

   In a discussion of the basic principles of system evaluation applicable to foreshortened intensive methods, Stokes (1942) wrote as follows

   Any new systems proposed should be judged basically by their ability (a) to equal or surpass the curative expectancy of the old ones, (b) to lead to less infectious relapse (c) to cure more mothers and protect more children, (d) to reduce the incidence of cardiovascular and neurosyphilis and (e) by their relative risks to the patient.

   For the evaluation of a system, time and observation are necessary to establish reduction of or absence of relapses and progression. For the former two to four years, for the latter up to ten years is a reasonable observational requirement. For decision *on relapse the patient must be repeatedly and frequently observed*, for it is . . . come

and go affair For the evaluation of cure from a decade to a lifetime the longer the better is required.

A system which under such scrutiny has shown itself at least equal to its predecessors may then proceed to claim additional advantage and support for variety of reasons, including cheapness, rapidity controllability of the lapse factor because the whole job is finished in short time, aid in the widening of availability of treatment by making possible the treatment of more persons per unit of time, personnel and equipment. Such considerations are in the main secondary to those of control of infectiousness and real curative power

If the new system equals the old or surpasses it in all these particulars it has but one more hurdle to make before achieving priority While primum non nocere is losing some of its meaning in war-torn orld, there are still arch conservatives who are inclined to examine critically the bad effects, the complications of system. Of real importance t the victim are the risks involved, the chances of damage or of death from treatment in the case of disease which with none or very little treatment gives the victim at the outset 40 to 70 per cent chance of escape from serious consequences. If an equal chance of escape with an older method offering less risk exists, only the most cogent reasons and free choice by the patient justify the selection of the more dangerous method.

THE CONSERVATIVE OR PROLONGED STANDARDS OF TREATMENT FOR EARLY EARLY LATENT AND LATE LATENT SYPHILIS

It is now in order to summarize what may be called the official' or most widely authenticated and accepted systems for use in that phase of the disease which permits of systematization in procedure. While it is impossible, with the rapid changes taking place in syphilotherapy to predict how long such systems will have a following, it should be clearly understood that they are effective, and will do all that the foreshortened systems will with a very much greater margin of safety To the British-Scandinavian intermittent system (which must be exactly followed, diagram in hand) and a slight but now for American practice, "official" modification of the American continuous (League of Nations) system, the "30-60-03" is added the as yet unproved and unevaluated but rational "Army Plan" recommended to the Surgeons General by the National Research Council and publicized in Circular Letter 74 The conservative systems are still, we believe, the backbone of modern practice, the basis of much of our present knowledge of mechanism and effects, and likely to be displaced completely only by certain radical changes in the whole chemotherapeutic attack on the disease such as are affecting the pyogenic infections, gonorrhea, etc. (the sulfonamides, penicillin)

It is recommended that

(a) In cases hich remain or become serologically negative during, or by the end of the first course four such courses be administered, with intervals of three to five weeks between any two courses.

(b) In cases which have not become seronegative by the end of the first course, in addition to the amount of treatment shown in (a), further courses should be administered until the patient has received as minimum three beyond that which has ended with negative serum reactions. At the option of the individual clinician, this treatment may be prolonged as may be considered necessary

(c) Cases presenting signs of clinical relapse of an early type should be dealt with on principles similar to those enunciated in (b).

For nonpregnant females, treatment should be administered on the plan outlined for men, with the exception that the single dose of neoarsphenamine should be reduced by 0.15 Gm. and that of arsphenamine by 0.1 Gm.

In the event of any reduction in the amount of treatment being indicated, it is recommended that this be effected by reducing the number of arsenical injections rather than by reducing the individual dose or increasing the intervals.

Fig. 430A.

THE BRITISH-SCANDINAVIAN (LEAGUE OF NATIONS) SYSTEM

Plan of Unit Courses of Injection

Week	Neoarsphenamine (Gm.)	or	Arsphenamine (Gm.)	and	Insoluble Compound of Bismuth Containing Bismuth Metal* (Gm.)
1st	0 6 to 0 75	or	0 4 to 0 5	and	0 20 to 0 24
2nd	0 6 to 0 75	or	0 4 to 0 5	and	0 20 to 0 24
3rd	0 6 to 0 75	or	0 4 to 0 5	and	0 20 to 0 24
4th	0 6 to 0 75	or	0 4 to 0 5	and	0 20 to 0 24
5th	0 6 to 0 75	or	0 4 to 0 5	and	0 20 to 0 24
6th	0 6 to 0 75	or	0 4 to 0 5	and	0 20 to 0 24
7th	0 6 to 0 75	or	0 4 to 0 5	and	0 20 to 0 24
8th	0 6 to 0 75	or	0 4 to 0 5	and	0 20 to 0 24
9th					0 20 to 0 24
10th					0 20 to 0 24

By insoluble bismuth is here meant compounds of a very slight solubility in water They should therefore be given in suspension, those of extremely slight solubility (the oxychloride, etc.) usually in a watery suspension, those that are more soluble (the subsalicylate, quinine bismuth iodide, the alkaline tartrates, etc.) suspended in a vegetable oil. If a liposoluble compound (e g the camphocarboxylat etc.) is preferred, it is desirable that the injection be given twice weekly in half doses.

The dosage of all bismuth compounds should be calculated according t their content in bismuth metal.

As an alternative t bismuth, course of mercury may be given, either in the form of inunctions (forty days t 3 Gm of unguentum hydrargyri) or of injections (70 mg. of mild mercurous chloride or 120 mg. of mercuric salicylat etc. suspended in suitable base)

League of Nations Investigation and Report on Treatment of Early Syphilis, Committee of Experts on Syphilis and Cognate Subjects, Zurich, November 21–23, 1934. Journal A.M.A., Vol. 104, No. 15, April 13, 1935.

THE AMERICAN CONTINUOUS SYSTEM

The 30–60–03" 'Official Modification (Circular Letter 18, Surgeon General's Office, U S. Army)—The published work of the United States Public Health Service and the Cooperative Clinical Group in the United States has indicated that continuous treatment with an effective arsenical alternating with bismuth on a definitely defined schedule with calendar regularity and without rest periods during the arsenical phase is the optimum conservative technic for the treatment of seronegative and seropositive primary syphilis, secondary syphilis, and early latency (within the first four years of the infection when the duration is known) An essentially similar standard of treatment employing 606 parallel with an acceptable intermittent (British-Scandinavian) system of treatment employing neoarsphenamine, has been recommended by the Commission on Syphilis and Cognate Subjects of the League of Nations as a result of an extended study of an international statistical material. It may therefore, it is believed, be accepted as having the support of authority

For mnemonic convenience the designation, "30–60–03" is suggested, for the standard system for early and early latent syphilis the "30" repre-

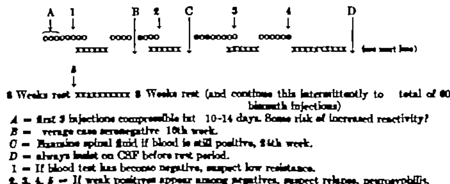
senting the number of arsenical injections the 60 representing the number of weeks of bismuth therapy equivalent to 60 injections of bismuth subsalicylate and the "0" and "3 representing respectively no rest periods, and three years of combined treatment observation. By "treatment observation" is meant the total elapsed time from the institution of treatment in accordance with this schedule until the patient is discharged from observation as presumptively cured

Since the sequence of various types of treatment in this system, the prevention of relapse by overlapping of heavy metal and arsenical therapy the serologic controls, the spinal fluid examinations, all are integral parts of the treatment system, the following diagram is offered as presenting these various relationships.

Fig. 439B.

The "30-60-03" for Early Syphilis

Thirty neoarsphenamine or mapharsen injections, sixty weeks of bismuth injections. No rest intervals in the arsenical phase, three years of treatment observation. O = neoarsphenamine or mapharsen; X = bismuth subsalicylate; weekly intervals.



8 Weeks rest xxxxxxxxxx 8 Weeks rest (and continue this intermittently to   total of 60 bismuth injections)

A = first 2 injections compressible int 10–14 days. Some risk of increased reactivity?
B = verage case seronegative 10th week.
C = Examine spinal fluid if blood is still positive, 24th week.
D = always insist on CSF before rest period.
1 = If blood test has become negative, suspect low resistance.
2, 3, 4, 5 = If weak positives appear among negatives, suspect relapse, neurosyphilis.

The "30-60-03" schedule as thus presented can be drawn up in "vertical" as distinguished from the above "horizontal" arrangement, week by   eek, for printing directly on record forms.

The published observations of the USPHS-CCG group on the treatment of early syphilis indicated that the "30-60-03" schedule could be most effectively pplied t seronegative primary syphilis and fully developed secondary syphilis. In the case of seropositive primary syphilis, whose status should be confirmed in the case of seronegative cases by a repetition of the blood test on the *day following the first arsenical injection*, there were definite indications that the seropositive primary phase of the disease lacking the development of a full-fledged immunity reaction on the part of the body was the most resistant to cure and the most prone to relapse of the three groups of cases included under the designation, early syphilis. It has accordingly been proposed that in seropositive primary syphilis and initially negative primary syphilis which becomes seropositive on the blood immediately following the institution of treatment, a 40–80–04 system be employed, meaning thereby an additional 10 arsenical injections and 20 bismuth injections and another year of observation over and above the standards proposed as generally applicable to early and early latent syphilis. This extension of the arsenical phase of treatment can take the form of five courses of the arsenical of eight injections each, in place of the three courses of eight and one course of six injections in the "30–60–03" system. The bismuth therapy may follow the usual two-injection overlap, plus four additional injections in the arsenical intermission that is employed in the "30-60-03"; the remaining bismuth injections to complete the 80-week standard, being continued in 10-injection intermittent courses after the completion of the arsenical phase of treatment.

Fig. 439C.

THE 26-WEEK ARMY SYSTEM

The 26-Week Army System for Early and Latent Cases.—This diagram is adapted from Circular Letter 74 Surgeon General's Office U S. Army

Week	Arsenoxide	Week	Bismuth
1		1	
2		2	
3		3	Bismuth subsalicylate intramuscularly once a week. 5 injections.
4		4	
5	Arsenoxide intravenously twice week. Total 20 injections.	5	
6		6	
7		7	
8		8	Omit bismuth subsalicylate. 5 weeks.
9		9	
10		10	
11		11	
12		12	
13		13	Bismuth subsalicylate once a week. 6 injections.
14	Omit arsenoxide 6 weeks.	14	
15		15	
16		16	
17		17	
18		18	
19		19	Omit bismuth subsalicylate 5 weeks.
20		20	
21	Arsenoxide as in first course twice eek. Total 20 injections.	21	
22		22	
23		23	
24		24	Bismuth subsalicylate once a week. 5 injections.
25		25	
26		26	

Dosage 0.05 to 0.07 Gm. arsenoxide based on patient weight. 0.2 Gm. bismuth subsalicylate. (40 injections arsenoxide—16 bismuth subsalicylate.)

Serologic Control of Treatment. In patients with early syphilis serologic test ill be done at the beginning and end of the schedule of treatment outlined in Fig. 439C but treatment may be stopped whether the serologic eaction for syphilis is positive or negative. After the completion of treatment the serologic tests should be repeated three and six months later If the reaction is negative after six months, the case may be classified as result satisfactory and the *Syphilis Register* may be closed. If the reaction is positive after six months, the patient should be referred to a station or general hospital.

In patients with latent syphilis the serologic tests should be repeated at the completion of the treatment outlined, but the *Syphilis Register* may be closed when this treatment is completed, regardless of the result of the serologic test.

Spinal fluid examination should be performed in hospital in patients with early syphilis t the end of the course of treatment outlined in Fig. 439C, or as soon as possible thereafter but in any event before the Syphilis Register is closed. I pparent latent syphilis, spinal puncture should be performed in hospital before treatment or as soon as possible thereafter but in any event before the *Syphilis Register* is closed.

A SYSTEM OF TREATMENT FOR LATENCY

'24-60-100 plus. —Before defining a system by which adequate treatment of latency may be judged, it must be reemphasized (see Chapter X)

that the latency here implied is "monosymptomatic seropositive latency" in which absolutely no clinical evidence of syphilis can be identified on complete physical examination except the positive confirmed and confirmable blood serologic reaction for the disease. An adequate examination of the spinal fluid is necessary to establish the fact that a seeming latency is not complicated by asymptomatic neurosyphilis. A patient who has been adequately treated for an early syphilitic infection but who still remains seropositive on the blood in order to be considered in monosymptomatic seropositive latency (serologically fast) should have had a negative spinal fluid one year after the close of his treatment for early syphilis, and if more than a year has elapsed since the cessation of such treatment, a repetition of the spinal fluid examination is desirable A long series of negative spinal fluids is not necessary to the establishment of the status of monosymptomatic seropositive latency for according to CCG observation, more than one or two repetitions of a negative fluid in the absence of any developing clinical signs is unnecessary

The latency of a syphilitic infection is divided arbitrarily into an early and a late period, partly because of the greater risk of infectious relapse and other types of recurrence in early latency and partly because of the presumed better outlook for complete arrest if not cured in the earlier years of the latent period The dividing line between early and late latency has tended in American practice to be the fourth year of the disease. This is an arbitrary setting which may in the judgment of an expert, be varied one way or the other A young and robust person whose infection is of five or even six years presumed duration, may be advised to accept the standard for an early infection in his treatment. On the other hand, most genuine latency after the fourth year shows relatively little tendency to progression and may be treated by a standard substantially lower than that proposed for the radical cure of early infection.

The treatment of early latency (first four years of the disease) is that of early syphilis—the "30–60–03" system.

The Cooperative Clinical Group's experience (Moore as spokesman) has indicated that for the treatment of late latency (after the fourth year) three courses of eight injections each of an effective arsenical given in continuity and alternation with ten injections of bismuth subsalicylate without overlap and with continuity extending only through the arsenical phase, constitute an adequate beginning The continuous treatment with arsenical and heavy *metal is then followed by an intermittent and* prolonged treatment with bismuth alone which should total, including the three 10-injection bismuth courses given with the arsenical phase, not less than 60 weeks of bismuth therapy Further treatment with bismuth to the extent of 80 weeks, or even 100 weeks, or on the basis of 80 weeks, plus a course a year" for several years, was found to increase appreciably the good results by the criteria employed

It is not necessary however in judging candidates for admission to the services, to insist on prolongation of the heavy metal phase beyond the 60th week. Approximately 70 per cent of monosymptomatic seropositive latency may be expected to reverse to negative on the blood for an indefinite period following a 24–60 course and the failure of the remaining 30 per cent to reverse may be regarded as no bar to eligibility

As a general principle, late latent cases remaining seropositive after a 24–60 course should be observed at intervals of a year or two with physical

examination and appropriate tests for evidence of cardiovascular progression and ultimate neurosyphilitic involvement.

It should be emphasized that late latency is usually much over-treated on the basis of fluctuating positive blood serologic tests alone, or because of conflicts between the results of various laboratories, "serologic discord." The trend of opinion downward, in the form of less and less exacting demands for the treatment of late latency has been largely under the influence of Moore and his associates, whose re-examinations of latent patients (Diseker Clark and Moore) based on 926 patients with latent syphilis followed for five years or longer led to the following statement

1 Latent syphilitics do very well regardless of the type or amount of treatment received.
2 The optimum amount of treatment to reduce progression to a minimum is approximately 20 injections each of an arsenical and a heavy metal.
3 The over-all rate of clinical "cure" with optimum treatment is about 95 per cent.
4 Clinical and serologic cure in latent syphilis have no relationship

MASSIVE DOSE, FORESHORTENED CHEMOTHERAPY OF EARLY SYPHILIS

Description of Procedure, Indications and Contraindications

All methods of intensive therapy are intended for patients with early syphilis (primary secondary relapsing secondary and early latency) who have received little or no previous therapy who are robust young people, especially men, reasonably free from serious visceral disease, particularly hepatitis, myocarditis, severe hypertension, nephritis, excessive alcoholism, blood dyscrasias, active pulmonary tuberculosis, and history of previous serious arsenical reaction. Although it is safe to administer sulfonamides simultaneously with conservative prolonged therapy and even with the twelve-week system it is unsafe to give sulfonamide therapy for gonorrhea or other conditions to patients receiving five to ten day intensive therapy

Addition of Bismuth to Massive Dose Technic—Since July 1941 L. W Shaffer has been using bismuth concurrently with the arsenical. It may be used as follows

Dosage of Bismuth with Intravenous Drip Method.

1 A suspension of bismuth subsalicylate in oil is employed.
2. The patient should receive 0.2 Gm. bismuth subsalicylate (0.13 Gm. bismuth metal) intramuscularly as soon as the diagnosis of early syphilis is confirmed.
3 The second dose of 0.2 Gm. should be given on the third day of treatment, the third dose of 0.2 Gm. on the sixth day and fourth dose of 0 2 Gm. on the ninth day before discharge.

Method of Preparing Mapharsen Solutions. 0.01 Gm. mapharsen (arsenoxide) is dissolved in 100 cc. of 5 per cent dextrose solution. Usual procedure is to prepare 600 cc. of such solution, containing 0 06 Gm. mapharsen—this is enough for three hours of treatment.

When the Vacoliter containing 2000 cc. of 5 per cent dextrose is used, the total daily dose of 0.24 Gm. of mapharsen (arsenoxide) is prepared the first thing in the morning and the solution allowed to run in, in the ten- t twelve-hour treatment period.

This has been the practice in one institution. The preparation of the drug for the ten- to twelve-hour period all at once has simplified the technic to great extent.

Variants in Usual Procedure

1 Primary fever on the first day (Herxheimer)—therapy is stopped if temperature reaches 101 4 or more. This usually happens between the 6th and 8th hour by this time patient may

Fig 440.

PRETREATMENT ROUTINE (ALL METHODS OF INTENSIVE CHEMOTHERAPY)
(After Leder 1940)

1. Urinalysis, including determination of urobilin. Urinalysis repeated daily
2. Determinations of the urea nitrogen content of the blood and the icterus index.
3. Complete blood count, including that of the platelets.
4. Complete physical examination on admission.
5. Serologic examinations made in three different laboratories (these include the Kolmer Kline diagnostic, Kline exclusion, Kahn standard and titered Wassermann tests)
6. Darkfield examination of material from all open sores.
7. Estimation of renal function by determination of the specific gravity of the urine.
8. Special tests of hepatic function by the bilirubin method.
9. Studies of the excretion of arsenic in the urine and in the stool and its concentration in the blood. (Optional for study purposes.)

Fig. 441.

TECHNIC OF 5-DAY INTRAVENOUS DRIP (Hyman, Chargin, Leifer) (After Committee on Massive Drip Intravenous Therapy 1940)

Materials

1. Needle—deep injection type #20, 1½ inch length.
2. Diluent—5 per cent dextrose solution.
3. Drug—mapharsen (arsenoxide) ampules 0.04, 0.06, and 0.6 Gm.
4. Glass gravity cylinder 300 cc. capacity with attached rubber tubing, glass drip chamber adapter for needle. (See Illustration. Vacoliter or similar container may be used instead of apparatus described. (L. W Shaffer))
5. Adhesive or scotch tape (one-half inch width).

Dosage of Mapharsen.

1. Total dosage for the five-day treatment period is determined by the stripped weight of the patient, in patients weighing less than 70 Kg. (155 lbs.) the total dose is 1000 mg (1.0 Gm.) In those weighing 70 kg. (155 lbs.) or more, the total dose of arsenoxide is 1200 mg. (1.2 Gm.)
2. The daily dose is 200 mg. (0.2 Gm.) for patients receiving a total of 1000 mg. (1.0 Gm.).
3. The daily dose is 240 mg. (0.24 Gm.) for patients receiving a total of 1200 mg. (1.2 Gm.)
4. If a patient receives less than the intended daily dose (this will most often occur on the first day of therapy) the deficiency in dosage may then be spread over the remaining days of treatment. Thus, if the patient receives 120 mg (0.12 Gm.) the first day instead of the intended total daily dosage of 240 mg. (0.24 Gm.) he may be given 30 mg. (0.03 Gm.) additional on each of the succeeding four days of treatment.

Procedure: Site of election for insertion of needle (see Fig. 442) After cleansing of forearm and application of a tourniquet above the elbow to distend the veins, the needle is attached to a 2 cc. Luer-type syringe and inserted in a vein on the forearm, usually anterior or outer aspect, between elbow and wrist, to allow movement at these articulations. Needle should be inserted into vein up to the hub, a gauze sponge placed beneath the needle hub, and the needle fixed in place with adhesive (or scotch tape). Alternate arms used on succeeding days.

The adapter of the intravenous set is attached to the needle (after the adapter has been freed of air bubbles) after the removal of the tourniquet, and the solution is allowed to flow rapidly until 10–15 cc. has entered. Should any swelling or infiltration be noted about the needle point, the flow should be stopped; the needle removed, and reintroduced into a different vein in the same or opposite forearm. (Refer to diagram (Fig. 442) and note manner in which tubing is looped on the forearm and taped so that these become a part of the forearm.")

The rate of flow is regulated by the fine adjustment clamp so that solution enters at a speed of about 30–60 drops per minute: thus, the entire quantity of 2000 cc. will require eight to ten hours for introduction.

have received only from 0 12 Gm. t 0 16 Gm. mapharsen. The practice has been t compensate for this insufficient dose in the following manner

First day—0 12 Gm. mapharsen (arsenoxide)
Second day—0.28 Gm. mapharsen (arsenoxide)
Third day—0.28 Gm. mapharsen (arsenoxide)
Fourth day—0.28 Gm. mapharsen (arsenoxide)
Fifth day—0.24 Gm. mapharsen (arsenoxide)

2. Clinical jaundice—when this appears in the course of treatment, the procedure should be interrupted It has only been seen once in all cases studied (Committee report)

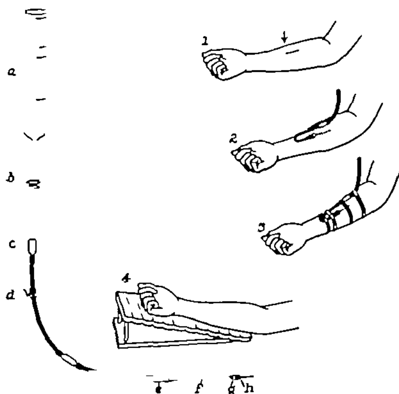


FIG. 442 —SCHEMATIC SET U FOR MASSIVE-DOSE ARSENOTHERAPY (5-DAY DRIP).

( ) 500-cc. graduat cylinder (elevation 2½–3 ft. above level of arm) (b) Murphy clamp (fine adjustment of flow) (c) drip bottle (d) spring clamp (to quickly shut off flow) ( ) glass window (f) finer rubber tubing (g) adapter (h) 20-gauge 1½-inch needle.

1 Site of injection—needle inserted t lnab (bet een elbow and wrist) 2, needle hub, tubing and glass adapter taped firmly ith adhesive so that these become part of forearm (see 3); 3, t show arrangement of drip after insertion of needle 4 arm board—padded for arm rest. (After William Leifer Courtesy of the Committee on Massive Drip Intravenous Therapy)

General Medical Care During 5-Day Intravenous Drip

According t Leifer (1940) description The nursing problems during the period of treatment consists of the preparation of fresh solution for each patient at the end of two or three hours and the refilling of the gravity flask. Meals are served on the ordinary bed tray Patients ca feed themselves. They are also capable of handling the urinal but, naturally must be assisted somewhat in the use of the bedpan. The latter disturbance may be prevented by having the patient evacuate or have an enema during the evening, when treatment has been discontinued.

The patients are given high caloric diet, rich in starches and carbohydrates. The majority of the patient read, listen to the radio or play cards during the day I the evening after discontinuance of therapy they may get out of bed. They suffer little or no discomfort. Many of them register gain in weight of as much as 10 pounds (4.5 kg.). This gain in weight is not d

to any appreciable edema but may be explained by the fact that most of these patients, other wise undernourished are so well treated with regard to food and nursing care.

TECHNIC OF 10-DAY MULTIPLE INJECTION INTENSIVE THERAPY FOR SYPHILIS (Schoch; Thomas)

With this treatment system patients need not be confined to bed but they should be treated in the hospital and observed for at least two days after the last injection of mapharsen (arsenoxide) Routine ward diet may be employed.

T injections of mapharsen (arsenoxide) are given daily for ten day period. The injections are given in the morning and evening of each day ten, or preferably twelve hours apart. Schoch, however has given single injections of 100 t 120 mg daily as an ambulatory procedure. Dosage is governed roughly by eight. Patients weighing 50 to 70 kg (110 to 154 pounds) should receive 0.05 Gm. of mapharsen twice daily for ten days. Patients weighing between 70 and 90 kg (155 t 200 pounds) should receive 0.06 Gm. of mapharsen twice daily for ten days. The dosage may be increased to 0.070 Gm. in each injection for patients weighing over 90 kg. (200 pounds) Each dose of mapharsen (arsenoxide) should be dissolved in from 5 to 10 cc. of distilled water The *solution should be aerated* and *rapidly injected* intravenously promptly after preparation. In cases where solutions are made in bulk, individual doses should be given within at least two-hour period after preparation.

On th first, fourth, eighth and twelfth days, 0.2 Gm. of bismuth subsalicylate in oil should be injected deeply into alternate gluteal muscles.

Thomas and his associates of Bellevue Hospital combine fever therapy with the intensive multiple syringe technic (1941 1943) The risk of serious cerebral accidents with this method increases with the amount of arsenoxide (mapharsen) given. The addition of fever does not prevent cerebral reactions but lessens their frequency by necessitating lower dosage of arsenical.

REACTIONS FROM 5-10 DAY INTENSIVE THERAPY AND THEIR MANAGEMENT

Minor Reactions

1 *Pain in the arm* Cold wet dressings, ice-bag aspirin codein only if pain is severe.

2 *Mild headache* Aspirin or codeine usually gives prompt relief If headache is severe, increasing and persistent, consider this as possible prodrome of toxic encephalopathy

3 *Nausea and vomiting* Give only fluids by mouth, and sedation if necessary If persistent, discontinue treatment temporarily May give 5 per cent or 10 per cent dextrose solution alone intravenously

4 *Primary Fever* Sharp rise in temperature occurs on the first day of treat ment especially with intravenous drip It is usually almost normal by evening and normal by the next day If the temperature goes above 101.4 F discontinue drip for the day Next day drip may be reinstituted, practically always without recurrence of fever This early fever need not cause omission of the second dose when multiple syringe method is used. Primary fever is usually accompanied by a flare-up of the syphilitic lesions (Herxheimer reaction or therapeutic shock) Symptomatic treatment may be used if necessary

5 *Secondary fever* Secondary rises of temperature in excess of 101 F at any time after the first day of treatment are an indication for inter rupting therapy because secondary fever is sometimes associated with a mild toxicoderma. Most often in the five-day treatment the fever occurs on the last evening of therapy Mapharsen should not be given again until the temperature is normal. If fever recurs when treatment

is reinstituted, efforts at intensive therapy should be abandoned entirely

If the patient has received at least a total of 800 mg (0.8 gm) of mapharsen (arsenoxide) before the appearance of fever intensive arsenotherapy by any system should not be reinstituted. In this case all further arsenical therapy may be omitted but the patient should receive a total of at least 12 weekly intramuscular injections of bismuth subsalicylate before all treatment is stopped

Symptomatic treatment for this reaction may be used if necessary

6 *Toxicoderma* Usually appears in the post treatment period on the seventh day and is often preceded by and accompanied with fever The type is most commonly morbilliform, scarlatiniform or urticarial, and there is no exfoliation. This is not arsenical exfoliative dermatitis, and is not a serious sensitizing reaction. The rash usually fades in one and one-half to four days without therapy Symptomatic treatment may be used, when indicated

Since this reaction does not usually occur with the intravenous drip method until all treatment has been completed, it has no bearing on interruption of such treatment. When the ten-day multiple injection system is used, the occurrence of this "ninth-day erythema" is an indication for interrupting treatment. This reaction may be associated (rarely) with toxic encephalopathy and continued treatment may increase the risk.

7 *Renal damage* Usually insignificant, consisting of minor traces of albumin, occasional red and white blood cells. No treatment is needed. Marked albuminuria or hematuria is a signal for discontinuing treatment.

8 *Peripheral neuritis* Rarely encountered, and only in the post-treatment period. Usually manifested only by subjective symptoms, most often paraesthesias. Objective changes are rare and only sensory in type, never motor The process disappears spontaneously This reaction was common in the cases treated early in the five-day method, probably because of immobility of the arm and the use of a drug too toxic (neoarsphenamine) for such a method.

9 *Nitritoid reaction* Rarely observed with multiple injections or with the intravenous drip procedure, unless the rate of flow of the latter is inordinately fast (mapharsen is well known to produce this reaction only rarely)

10 *Precordial oppression.* (Falk and Rattner 1942 Prats, Varas, and Harasti, 1942) This occurs occasionally with five-day treatment. Disconcerting but not frequent or serious.

Major Reactions

1 *Severe headache* Especially towards the fourth or fifth day of treatment, the occurrence of severe, persistent and increasing headache not readily relieved by aspirin or codeine, should be viewed as of possible serious import (prodrome of toxic encephalopathy) It is best to discontinue intensive therapy and after a rest interval from all arsenical therapy of at least four weeks (this rest period to be occupied with weekly bismuth injections) to place the patient on the standard or twenty-six week treatment schedule the duration of which may be shortened to the ex

tent of the mapharsen dosage before the reaction occurred (e g., if the patient received a total of 400 mg. mapharsen before the reaction 1200 mg additional should be given by injections twice weekly with bismuth added as in the standard schedule)

2 *Jaundice* This is an uncommon complication and calls for discontinuance of intensive therapy No instance of acute yellow atrophy has occurred although Rattner and Falk (1942) observed a case of severe hepatitis with other visceral damage (see below)

For the treatment of the reaction, the patient may be given intravenous 10 per cent dextrose solution high carbohydrate-low fat diet, and injections of liver extract therapeutically Intestinal elimination should be encouraged with saline catharsis.

3 *Blood dyscrasias (especially purpura or bleeding from any part of the body)* Rarely encountered, but necessitating permanent discontinuance of all arsenotherapy Treatment usually consists of blood transfusions.

4 *Exfoliative dermatitis* Rarely if ever encountered. Requires permanent discontinuance of all arsenotherapy Symptomatic treatment, dextrose intravenously and liver extract.

5 *Encephalopathy* Women are especially susceptible. This reaction may be manifested by severe headache, vertigo, tremor fever unusually severe nausea and vomiting, mental confusion, disorientation, and apathy· by single or repeated convulsive seizures, and by prolonged chorea. In serious instances hyperthermia usually supervenes and *death* may result. May occur on the third to fifth day of treatment, or not until the sixth or seventh day rarely thereafter Often preceded by headache of increasing severity (see above) There is no means of anticipating this reaction (Thomas, Wexler and Dattner 1942)

In mild cases, the suspicion of toxic encephalopathy should be checked by examination of the spinal fluid for cells, globulin or increased protein If such tests are positive, further treatment with arsenical drugs should be abandoned. If the spinal fluid is normal, treatment may be resumed if the symptoms have completely disappeared and the temperature is normal.

Treatment of this serious reaction is of uncertain value but the prognosis is not as bad as is usually assumed (Chargin 1940) Suggested procedures include (1) repeated drainage of spinal fluid (20 to 40 cc.) in repeated taps daily (2) dehydration by use of intravenous 50 per cent sucrose solution 50 to 200 cc. (3) sedation is of value in all cases. Where symptoms are mild, any of the barbiturates may be used by mouth. If convulsions occur sodium amytal 0.24 Gm. (3¾ grains) may be given intravenously or intramuscularly (this dose may be repeated every two to three hours for several doses if convulsions occur or the patient is restless for use of adrenalin see p 435 Oxygen inhalations should also be given. Sodium thiosulphate is of no value (Chargin, 1940)

6 *Severe renal injury* (rare) Thomas and his colleagues (1943) have reported acute nephrosis in patients receiving short arsenical and prolonged fever treatment but no particular renal damage occurs in their patients treated with the multiple injection method (ten or six days) Rattner and Falk (1942) reported a severe case with acute glomerulonephritis, anuria, uremia, hepatitis ileus and pericarditis in a patient treated by the five-day method.

Post Treatment Routine after 8–10 Day Intensive Therapy (to be carried out before discharge from hospital).

1 Complete physical examination.
2. Laboratory studies:
   (a) Titered blood serologic test for syphilis.
   (b) Complet urine analysis.
   (c) Complet blood count (hemoglobin, red blood cell and whit blood cell count and differential)
   (d) Other laboratory procedures (icteric index, serum bilirubin, urobilinogen, non-protein nitrogen) where indicated.

OUTLINE OF PROPOSED 12 WEEK SCHEDULE OF MODIFIED INTENSIVE TREATMENT (Eagle, 1943)

Patients are to be treated with mapharsen (arsenoxide) three times weekly (Monday Wednesday and Friday or Tuesday Thursday and Saturday) at the following dosage scale —

Less than 120 lbs. (55 kg.)	50 mg.
120–155 lbs. (55–70 kg)	60 mg
Greater than 155 lbs.	70 mg

Treatment is to continue for twelve weeks or a total of 36 injections. Hospitalization is not necessary and patients are to be treated on "duty status."

Patients are to receive intramuscular injections of bismuth subsalicylate (0.2 Gm., equivalent to 0 13 Gm. of metallic bismuth) once weekly throughout the course of mapharsen (arsenoxide) treatment, to a total of 12 injections

Fig 445.

FOLLOW-UP OBSERVATION AFTER ALL METHODS OF INTENSIVE CHEMOTHERAPY

1 Patient should be reexamined t monthly intervals for six months.
2. This reexamination should include a complete physical examination with special attention to the mucous membranes of the mouth and throat, the genitals and the perianal region for early overlooked evidences of infectious elapse
3. A quantitative blood serologic test for syphilis should be performed monthly for six months, and then t the 9th and 12th month. (The blood serologic reactions usually become negative t the 12th–16th week after the start of treatment)
4. Examination of the spinal fluid should be done if feasible, sometime between the 6th and 12th month.
5. The patient should not receive any further antisyphilitic therapy except as specifically set forth under management of the unsatisfactory case

MANAGEMENT OF THE UNSATISFACTORY CASE

A patient who has become clinically "cured" and serologically negative and remained so until the twelfth month of observation, and in whom the spinal fluid is negative, may be discharged from observation as a "*satisfactory* result." Should such a person return at a later date with a new darkfield positive lesion, this may be considered as a new infection and the patient may be retreated in the original manner (Schoch, 1945, Moore, 1945 L. W Shaffer 1945) See discussion of Reinfection p. 185

A case must be considered as unsatisfactory or a treatment failure, if

1 There is definite objective evidence of infectious relapse, corroborated by positive blood serologic reaction for syphilis, and if possible by positive darkfield examination.
2. There is incontrovertible evidence of serologic relapse without clinical relapse, i.e., the patient blood serologic test has dropped to negative or near negative and then to persistently strongly positive (this is best interpreted by a quantitative procedure)
3. Reagin fastness, i.e., where the blood serologic reaction for syphilis has never reverted to negative but remains persistently positive (preferably determined by constant titer of quantitative tests) for six months period after treatment.

The unsatisfactory case (infectious relapse, serologic relapse, seroresistance) and the new infection may be retreated by intensive therapy except in the event of serious reaction from the original treatment.

The results of intensive retreatment of the unsatisfactory case have not been fully evaluated, but appear to be less satisfactory than original treatment.

ADDITIONAL SPECIAL CONSIDERATIONS CONCERNING EARLY SYPHILIS TREATMENT

Criteria of Adequacy of Treatment for Syphilis.—The answer to this question depends fundamentally upon the definition of "adequacy" If by adequacy is meant the securing of a condition of noninfectiousness in an infectious case, one kind of answer will be appropriate if adequacy is to be interpreted in terms of clinical or of radical cure, another answer will be appropriate if adequacy means the placing of an infected individual at one or another type or stage of involvement in syphilis on a symptomatic status that will permit of full or limited service in the armed forces, still another answer is necessary The subject is dealt with under each of these three heads briefly as follows

Treatment to Noninfectiousness.—The immediate infectiousness of surface lesions of syphilis is controlled in all but the rare treatment resistant or arsenic-fast case, it will be recalled, by the first one, or at most, two, injections of an effective trivalent arsenical provided the dose is adequate (0.3 to 0.5 Gm arsphenamine 606 0 4 to 0 6 Gm. neoarsphenamine 40 to 60 milligrams mapharsen. The duration of this effect of one or two injections is not precisely known, but is estimated roughly as approximately thirty to ninety days. Failure to continue treatment does not necessarily but may in a percentage of cases ranging from 0 to 64 per cent, lead to infectious relapse. A useful tabulation from Cooperative Clinical Group and University of Pennsylvania material is herewith presented

Fig 444

Arsenical treatment alone, number of injections.	Infectious relapse, per cent.	Additional heavy metal injections.	Infectious relapse, per cent.
1 4	64	20†	45
5– 9	14	20	9
10–19		20	4
20–29		20	3 6
26 5*		29.2 or more	0
30–40 ..		"appropriate	1.2

* University of Pennsylvania figures; all others are C.C.G.
† One week of mercurial inunctions equals one injection.

From this tabulation it will be apparent that the critical point at which sharp reduction in the probability of recurrent infectiousness takes place is between the fifth and ninth injections of the arsenical (14 per cent relapse without and 9 per cent with heavy metal) and that the so-called 20–20 standard often quoted as adequate for treatment to noninfectiousness, reduces the risk of infectious relapse to 4 per cent, beyond which a slow reduction to 0 to 1.2 per cent is secured by prolonging treatment beyond 30 arsenical injections with 30 or more injections of heavy metal.

Heavy metal in the statistical table presented above, is taken to represent 0.2 Gm of an insoluble bismuth salt of not less than 57 per cent metallic content, or one week of mercurial inunctions, or its intramuscular equivalent in a water soluble or insoluble mercurial salt.

It will presently be apparent, therefore, that the best treatment to secure noninfectiousness is practically identical with the optimum treatment for the securing of "satisfactory results" or "cure"

The Influence of th Development of Secondaries on Relapse.—A very interesting and seemingly paradoxical situation was revealed in the comparison of serological with clinical relapse under treatment—a relation of particular importance because it might well form the basis for polemic discussion. The stage of syphilis at which treatment is begun influences the incidence of mucocutaneous relapse in different way from that in which it affects all other forms of relapse. The first Cooperative Clinical Group survey of mucocutaneous relapse as such (presented t the Copenhagen Congress) indicated that it occurs in 10 per cent of patients beginning treatment in the seronegative primary stage· 8.6 per cent of those beginning treatment in the seropositive primary stage and only 4.2 per cent in those who began treatment after their secondaries had fully developed. Relapse incidence of the mucocutaneous type was therefore markedly less if the patient was allowed to develop his full cutaneous secondary reaction to the disease, the difference amounting to as much as 58 per cent reduction in probability as the patient passed from seronegative primary to the florid secondary phase. On the other hand, the existence of distinct relapsing type was foreshadowed by the fact that patients who began treatment with late or recurrent secondaries relapsed in 24.3 per cent of cases. Serological relapse, on the other hand, occurred in 12 per cent of patients whose treatment was begun in seronegative primary syphilis· 10.2 per cent if the treatment as begun in seropositive primary syphilis; 18.1 per cent under the same circumstances in early secondary syphilis (first year) and 20 per cent if treatment was not begun until delayed secondaries after the first year It ppears, therefore that t begin the treatment of patient in the seronegative stage of primary syphilis, while it has already been shown definitely t increase the prospect of complet cure, none the less subjects him to definite slight risk of mucocutaneous recurrence and therefore of more prolonged infectiousness. The probable explanation, of course, is that the skin and mucous membranes have never been given the opportunity to develop what might be thought of as local tissue immunity by full reaction t the disease

It must of course be appreciated that the reduced incidence of relapse and progression in patients who have had secondaries arises simply from the fact that in reaching that stage they have automatically so to speak, set behind them that much of the life history of the disease It must, too, remain for further study to decide whether the increased risk of infectious recurrence after early treatment justifies postponement until the patient has developed secondaries. At the present time the higher proportion of curative results seems to justify immediate treatment rather than postponement. The increased risk of infectiousness through recurrence can hardly be greater than the risk of infectiousness represented by a patient allowed to live at large in the com

[1] The percentages estimated on the basis of 3244 cases observed and treated for six months or over were seronegative primary 16.4 per cent seropositive primary 20.8 per cent; secondary (first year) 9.3 per cent secondary delayed 9.2 per cent. The principle illustrated is the same in both.

munity without benefit of the arsphenamines until his secondary eruption has fully developed. In any event, the application of such a principle demands universal hospitalization for the patient between the primary stage and the full development of secondaries, an obvious impracticability at this time. Until the proponents of postponement (as for example, Bernard) can advance indubitable evidence that there is other than merely mucocutaneous protective value in permitting a patient to go on to secondaries, the postponement of treatment until secondaries develop is not only against the interests of the public health but against that of the individual patient, who above all things desires the greatest possibility of personal cure.

Jadassohn, from an international questionnaire, has reported that the effect of arsphenamine in controlling the infectiousness of syphilis has led to an estimated reduction in incidence of new cases of the disease of 75 to 80 per cent in Belgium, Sweden, and Holland; 60 per cent in Finland 50 per cent in Denmark; 40 to 50 per cent in Switzerland 20 to 60 per cent in Italy and Czechoslovakia; and 25 per cent in Norway

Rules for Preventing Infectious Relapse.—The prevention of infectious recurrence and the reduction of relapse to the lowest possible terms requires of the practitioner then, an unhesitating acceptance of the following rules (1) The concept of abortive cure by short courses should be abandoned, no matter how early the patient may come under treatment. (2) Not less than 20 injections of an arsphenamine, and more if possible, preferably in one or two courses, and an equivalent amount of heavy metal without rest intervals should be given in an early case to control infectiousness. (3) Treatment should be continuous rather than intermittent or intensive, there being no time, at least within the first year or more, that the patient is not under the influence of one or another effective mode of treatment for syphilis with an arsphenamine or heavy metal. (4) Treatment should be massed well to the fore—that is, within the first three months, for this is the period in which mass as distinguished from prolongation reaches its greatest effectiveness in preventing relapse. (*cf* massive dose arsenotherapy)

Stokes, Miller and Beerman in their study of bismuth arsphenamine sulphonat observed similar phenomenon. The proportion of relapse in continuously treated cases was 8 1 per cent and in those allowed rest intervals 14.3 per cent. Of the continuously treated patients, 60 per cent had comparatively little treatment (20 injections or less) while 66 per cent of the intermittently treated patients who had the higher incidence of relapse, had had comparatively heavy courses of 21 injections or more (40 per cent had over 40 injections) It appeared that smaller amount of treatment continuously applied yielded fewer relapses of all kinds than larger amount with rest periods or lapses.

With so much emphasis placed on the seriousness of lapse in the promotion of infectious recurrence, it is proper to emphasize as the fifth rule for the physician, (5) his responsibility in educating his patient and in holding him to a sufficiently prolonged course and in utilizing follow-up assistance if and when it is available. He should understand, too, that (6) infectious relapse is detected by actual physical examination with special emphasis on the mouth, anus, and genitalia rather than by serological tests. One should examine especially the lips, penis, scrotum and vulva. (7) Positive serological tests may warn of infectious relapse and confirm the diagnosis, but since they cannot be frequently applied, physical examination and instruction of the patient himself in the recognition of infectious lesions are the more important approaches. (8) Serological tests and stripped physical examinations,

to be of value in detecting relapse should, if anything be more frequently made after treatment is completed and the patient is put on observation than during treatment itself The opposite is common practice and this applies especially to the first two or three years of the disease. (9) Negative serological tests, as has been repeatedly emphasized are not proof of noninfectiousness, immediate or future. A negative Wassermann or Kahn reaction should not deceive the physician or patient into relaxing precautions (10) Treatment and time are the chief preventives of infectiousness. Since potentially infectious relapses occur overwhelmingly in the first two years of early syphilis, (11) sexual relations and intimate contact without absolute protection should be allowed only while the patient is under actual arsenical treatment. The duration of noninfectiousness when treatment is stopped before the twelfth injection of arsphenamine may not, apparently exceed one month.

Adequacy with Respect to 'Cure or 'Satisfactory Results."—Information on this subject is based on case material observed for not less than two, and upward to twenty years since the onset of the infection or the institution of treatment. Material of less than two years of observational control is fundamentally weak in its demonstration of the possibility of relapse since the first two years of infection are overwhelmingly those of relapse predisposition. On adequacy in the sense of satisfactory results," five groups of data will be quoted (a) Cooperative Clinical Group results in the treatment of early syphilis by a continuous alternating use of arsenical and heavy metal without rest periods, through sixty-five weeks of treatment observation (b) Johns Hopkins Hospital Syphilis Clinic (Padget spokesman) reporting on 551 patients completely re-examined five years or more after the termination of their original treatment for early syphilis (c) optimal treatment for early syphilis, one to twenty years observation Cannon reporting (d) a shortened twenty week system, Hood reporting on Johns Hopkins Hospital material (e) the five-day intensive intravenous drip arsenotherapy of syphilis (without the use of heavy metal) Leifer Chargin and Hyman, 1941 and Elliott, Baehr Shaffer Usher and Lough 1941 reporting

It is not possible at this time to offer more than speculative estimates on ten-day multiple syringe and ten to twelve-week intensive mapharsen-bismuth (Eagle-Hogan) systems which are under study

The Cooperative Clinical Group' standard treatment system experience indicates that for satisfactory results, treatment must be continuous and not intermittent or irregular and must combine the alternate use of an effective arsenical (mapharsen is not represented in this material) and bismuth. Striking reductions in effectiveness with occurrence of infection relapse progression of syphilitic manifestations, serologic relapse and seroresistance occur in all phases of early syphilis in which intermittence or irregularity is allowed to occur Disregarding the precise system of administration, the highest proportion of satisfactory result in seronegative primary syphilis was obtained with 10 to 19 injections of arsphenamine with accompanying heavy metal in seropositive primary syphilis, with 25 to 35 injections; in early secondary syphilis (seen in the first year) 20 to 29 injections. Higher rather than lower dosage of the arsphenamine is recommended. Failure to secure satisfactory result by 20 injections or less may be met by 10 additional injections, plus heavy metal, which may double the proportion of unsatisfactory outcomes reclaimed. The irreducible margin of failure in the treatment of early syphilis by older standards ranges from 4 per cent to 27 per cent, depending on method, stage at which treatment begins, adequacy of treatment during the first two years of the infection.

Johns Hopkins Syphilis Clinic, Padget reporting on a particularly valuable material because of the length of observation (over ten years in half the patients) showed clearly the importance to adequacy of treatment result, of the stage at which treatment is begun (82 per cent cure in seronegative primary syphilis, 68.8 per cent in secondary syphilis 58.7 per cent in early latent

syphilis). The poorest results, as in the Cooperative Clinical Group series, were observed among patients whose treatment was begun in the seropositive primary stage. Cure was obtained by 83.4 per cent of the patients whose treatment during the first six months was by a continuous system, and was increased to 90.4 per cent if treatment during the next six months was likewise continuous. It was shown that the final or "adequate" outcome depended in a directly quantitative fashion not only on the number of doses of the arsphenamine received, but also inversely upon the time span during which it was given. In other words, the more injections in the shorter time, the better the results. The development of early or intermediate relapse was found to be of grave prognostic significance.

Cannon found in a group of about six hundred patients treated with three standard arsphenamines, that arsphenamine 606 was incontestably superior to neoarsphenamine or silver arsphenamine, and that one year of regular and continuous treatment with the arsenical injections closely spaced (two- to three-day intervals in the first three to five weeks and at intervals of not less than one week thereafter) gave the highest proportion of satisfactory results. The difference between seronegative primary, seropositive primary and secondary syphilis was not more than 6 per cent.

The 20-20 Arsenical-Bismuth Simultaneous Injection Course. Hood Reporting.—This shortened system, not comparable because of longer intervals (weekly) with the twenty-six-week system of Circular Letter No. 74, utilizes weekly injections of mapharsen and simultaneous weekly intramuscular injections of an oil-suspended bismuth salt. The maximum period of observation (thirty-three months) was only sufficient to indicate that the proportion of unsatisfactory results in the form of seroresistance, serorelapse, clinical relapse and involvement of the central nervous system, amounting to 12.6 per cent of the observed series, was approximately that of unsatisfactory results obtained in early syphilis treated with other arsenical drugs and treatment systems. If confirmed by longer observation, such a treatment system should show how little rather than how much treatment is necessary to produce the average or so-called "standard" results which are so strikingly uniform throughout the entire range from five-day intravenous drip to sixty-five-week continuous combined therapy.

Massive Dose Arsenotherapy "Five-day Drip."—The two series, Leifer *et al.*, and Elliott *et al.*, the former with of course the longer series of observed cases, illustrate the following principles regarding adequacy:

(a) Curative results can be obtained with a trivalent arsenical alone (neoarsphenamine, mapharsen).

(b) Of the two, mapharsen because of its low reactivity is the drug of choice, and 1200 mg. administered in five days, the optimum dose.

(c) In seronegative primary syphilis, 90 per cent to 100 per cent pursue a satisfactory and uneventful course; without reference to type of drug or stage of disease, an aggregate of 81 per cent secured a satisfactory result in one five-day course and one retreatment in 15 cases raised the result to approximately 88 per cent for the entire series (Leifer *et al.*). Elliott and coworkers estimated their curative results as at least 85 per cent of all cases with early syphilis.

Adequacy of Treatment from the Standpoint of Service in the Armed Forces.—A tentative basis for evaluation proposed for admission of registrants with syphilis to the United States Army is as follows:

Registrants with (1) confirmed positive serologic tests for syphilis and no clinical manifestations of the disease or (2) with convincing histories of a trustworthy diagnosis of syphilis; or (3) of treatment for the disease on serologic or clinical grounds even though such evidence may possibly have been inadequate, may be considered for unlimited military service:

(a) Provided that a negative spinal fluid since infection and treatment has been reported from a trustworthy source; and

(b) Provided that in infections estimated to be of less than four years' duration, at least 30 to 40 arsenical and 40 to 60 insoluble bismuth or its equivalent injections with a minimum total of 75 injections have been given, with approximate continuity (no rest periods or lapses) during the first thirty weeks of treatment; and

(c) Provided that except as further qualified below in infections estimated to be of over four years' duration, at least 20 arsenical injections and 40 to 60 insoluble bismuth injections or its equivalent with a minimum total of 60 injections have been given in alternating courses, rest periods between consecutive courses not exceeding eight weeks, being allowable.

Evidence of duration of the infection shall be weighed by the examiner with due regard for the age, general venereal history and medical guidance of the registrant.

In infections of unknown duration it shall be presumed for classification purposes that those of registrants under twenty-six years of age are of less than four years duration, and over twenty-six years, of more than four years duration.

In congenital infections and in acquired infections of more than ten years' known duration, in which no clinical progression occurred since treatment was begun; and in which normal spinal fluid and negative physical examination is recorded not less than two years after treatment was terminated, the infection shall be regarded as quiescent, and the registrant eligible for unlimited military service provided the treatment in question shall have included 20 arsenical and 20 heavy metal injections.

For the determination of treatment, the signed statements of acceptable treatment sources administering it with total number of doses of each drug and approximate calendar dates of administration and available laboratory and clinical data shall be required as evidence.

The Prognostic Significance of Secondary and Serologic Relapse.—The following principles, based in the main upon the groups of material cited in connection with the *criteria of adequacy of treatment for syphilis*, are widely accepted. Early evidence of potentially unfavorable or relapsing course in an early syphilitic infection can be found in (*a*) failure of the primary or secondary lesions to heal under an arsenical therapy (*b*) continued presence of *Spirochaeta pallida* in the lesions after the employment of a known effective trivalent arsenical (these two groups constitute treatment resistant syphilis) (*c*) prematurely early reversal of a positive serologic reaction on the blood to negative (fourth to seventh week in seropositive primary or secondary syphilis) (*d*) failure of a positive serologic reaction on the blood to reverse to negative after the sixteenth week (in the intensive or five-day drip system reversal is ordinarily expected by quantitative tests between the tenth and eighteenth weeks after the institution of treatment but late secondaries may not reverse for many months even though "cured")

Cooperative Clinical Group results (Stokes and coworkers) (observation period too short) showed a relapse expectancy of 19 7 per cent including all forms, of which, when observed for more than six months, 12.1 per cent was mucocutaneous, 3 4 per cent asymptomatic neurosyphilis, 4 1 per cent symptomatic neurosyphilis, and 0.9 per cent cardiovascular syphilis.

The unfavorable prognostic significance of early and intermediate relapse was well brought out in Padget s series in which "cure was achieved in 73.2 per cent of 456 patients in whom no relapse was observed, whereas only 28.2 per cent of those sustaining an intermediate relapse achieved cure. Persistent seropositive reactions on the blood however occurred in 16 per cent of those who sustained no relapse, and in 10 3 per cent of those who underwent intermediate relapse. Late benign syphilis developed 8 times as frequently in relapsers as in nonrelapsers, cardiovascular syphilis 3.5 times as frequently neurosyphilis 6 times as frequently multiple late manifestations 7.5 times as frequently in relapsers as in nonrelapsers. The occurrence of weak positive serologic reactions on the blood appearing in the course of a series of negatives in treated early syphilis has been emphasized as of relapse significance by certain authors.

Significance of Seropositivity after Treatment Which Was Begun during Early Syphilis.—Certain aspects of relapsing and persistent seropositiveness after treatment begun in early syphilis have been indicated above *Broadly* speaking Padget s experience indicated that a residue of 14.0 per cent persistent serologic positiveness would appear in a series of early syphilitics on whom the otherwise satisfactory results he described had been secured In these cases there would be no manifestations such as abnormal spinal fluid cardiovascular disease visceral disease and so forth to accompany the per

sistent seropositiveness. The inclination would be, therefore, to rate it in these cases as without significance. Broadly speaking, persistence of a positive serologic reaction on the blood of early syphilitics under treatment by the older standard continuous systems was an indication of presence of asymptomatic neurosyphilis, and called for an examination of the spinal fluid immediately The more intensive foreshortened treatment systems seem so materially to have reduced the likelihood of the occurrence of asymptomatic neurosyphilis that the neurosyphilitic significance of persistent seropositivity will probably be greatly reduced by their use. In addition to asymptomatic neurosyphilis, syphilis of the cardiovascular system often coming to recognition five or more years after the cessation of treatment may be included in the prognostic significance of seropositiveness of a persistent type in early syphilis.

Moore and Padget in their nalysis of seroresistant syphilis (early) emphasize the seriousness of seroresistance in early syphilis and its relatively lesser significance in late syphilis. Twenty-three per cent of their seroresistant group sustained infectious relapse as against 5 per cent who secured prompt serologic reversal. Neurosyphilis occurs in 31 per cent of the seroresistant cases, but in only 16 per cent of those who sustain prompt reversal.

The Prevention of Cardiovascular Syphilis.—This is still the *terra incognita* of modern syphilology and the studies thus far summarized have thrown relatively little light upon it. Langer and others have attributed the increase in the incidence of aortitis since 1918 t the use of arsphenamine in the treatment of syphilis but our material on early syphilis, so far as it goes, fails to substantiate this belief, the incidence of recognizable aortic lesions not increasing materially in the period studied. It is, of course true that our study does not extend forward into the period of maximum recognition of this form of syphilis. Moore Danglade and Reisinger in considering Langer contention, believed that the apparent increase coincident with the use of arsphenamine in treatment is due rather to more accurat pathologic study with increasing knowledge of microscopical appearance of aortic syphilis. Progression of cardiovascular syphilis in spi of various methods of treatment occurred in 0.8 to 1.8 per cent of our patients. Warthin observation, which placed the incidence of aortic syphilis in syphilitic adults between 1909 and 1919 t 27.6 per cent, and between 1919 and 1929 at 26.8 per cent, further supports the view that raphenamine is not responsible for the apparently increasing incidence observed by Langer

THE PREVENTIVE TREATMENT OF EARLY NEUROSYPHILIS

The treatment of neurosyphilis is considered as a unit under Chapter XX. It must never be forgotten, however that the effective treatment of neurosyphilis rests on its early detection, and on the vigorous, determined and systematic application to early systemic syphilis of the methods described in this chapter Inadequate treatment is worse than no treatment since the incubation period of clinical neurosyphilis in the inadequately treated individual (11.6 years) is six years shorter than in those who receive no treatment (17 6 years) prior to the time their neurosyphilis became clinically recognizable (Kemp 1940) Where definite symptomatic neurosyphilis especially involving the cranial nerves is apparent when the patient comes under treatment, the necessity for bismuth preparation has been repeatedly emphasized and quarantine should be enforced, so to speak, if the patient is infectious, while this preparation is being carried out. The Cooperative Clinical Group studies indicated that a certain proportion of early neurosyphilis is inevitable in spite of either much or little treatment, this proportion amounting to from 6 to 7 per cent of patients. It is none the less true that by far the larger part of early asymptomatic neurosyphilis responds in the course of standard effective treatment. In 1747 spinal fluid examinations in the Cooperative Group series it will be recalled that 32.7 per cent were abnormal in the Wassermann test or cell count or both, and 67.3 per cent were negative It was found that regard

less of the system of treatment appraisal a great deal of effect in reversing slightly abnormal spinal fluids was produced even by a small amount of treatment. On the other hand this effect was much less striking with respect to the more markedly abnormal fluids, including those with positive serologic reactions and especially those with paretic or Type III formulae.

The difference between slight abnormality and marked abnormality is especially apparent in the paretic formulae. Under both systems of appraisal it is at least twice as difficult to reverse a paretic as any other markedly abnormal fluid under little or much treatment (little treatment, 30.8 per cent reversed *vs* 69.2 per cent which failed to reverse and much treatment 38 5 reversed *vs* 61.5 failed to reverse) This is true even when tryparsamide and malarial therapy results are included

Fig 445

THE DECALOGUE OF PREVENTION OF EARLY NEUROSYPHILIS

1 Never give single arsenical injections, short courses (3 t 4 injections) or mercury by mouth. Give 8 to 10 arsphenamine injections in the first course
2. N rest intervals. Have the patient on one or another effective form of treatment continuously the first year
3. Examine the spinal fluid before the end of the first year and in any case before rest period. Have the puncture correctly done, so that there will be no confusion about the cell count (no blood contamination)
4 Take slight rises in cell count (above 7) seriously especially if found after the patient has had some treatment.
5 Th appearance of paretic formula is serious. If it does not respond within eight weeks to intensification of treatment, the fluid examination being repeated, it calls for tryparsamide or fever therapy The later in the course of systematic, energetic treatment that this formula occurs, the more serious it is.
6 A esistant positiv blood serological test must be thought of as suggestive of early neurosyphilis, examine the spinal fluid.
7 A negative blood serological test does not make spinal fluid examination unnecessary
8. When possible hav the fundus of the eye examined early for signs of nerve involvement.
9 Signs in the fluid usually precede symptoms from the nervous system. Do not expect t detect early neurosyphilis by relying on reflex changes, abnormal pupils, etc. These are late neurosyphilis.
10 Remember that headach is significant but not conclusive and that spinal fluid may be normal, but the patient have or later develop, neurosyphilis.

Treatment-fast spinal fluids resisting all efforts to reverse them appeared in 1.3 per cent of the total number of patients seen and 5 8 per cent of the 730 abnormal spinal fluids. This is almost identical with the incidence of paresis from the clinical side in Bruusgaard s postmortem series of spontaneously evolving, untreated syphilitic patients.

It appeared finally that more irreversible spinal fluids developed among seropositive primary early secondary and delayed secondary cases than among seronegative primary cases, the per cent being 0 0 seronegative primary 1 0 seropositive primary 1.3 early secondary and 6 2 delayed secondary Thus it appears again that the institution of treatment in the seronegative primary stage has the most significant advantage of reducing the probability that the nervous system will be irremediably involved.

In Fig 445 are summarized the preventive principles applicable in early neurosyphilis. Details as to procedure are included in the chapter on Neurosyphilis.

CHAPTER XV

THE LANDMARKS OF LATE SYPHILIS ON SKIN AND MUCOUS MEMBRANES

Familiarity with the cutaneous lesions and scars of late syphilis is of great value to the diagnostician in that it serves in the first place to provide "suspicion arousers" in the case of patients whose general medical condition does not suggest syphilis, and, in the second place not infrequently provides sufficient evidence to clinch the diagnosis in the absence of that almost universal criterion of reference the positive blood serologic reaction. This latter function will, of course, vary in importance with the serological technic employed It is only fair to say that the proportion of negative blood serologic reactions observed in the ensuing case presentations is probably higher than we would now obtain with the Kolmer technic or other sensitive procedure. But the fact remains that the first, the chief or the only clue to a latent syphilitic infection or rather a relatively quiescent one, may lie in some lesion of skin or mucosae to which the patient has given little or no attention, and that a cutaneous or mucosal lesion, correctly interpreted may identify a syphilitic infection which would otherwise be missed because of anomalous signs or a negative serology

In the period of latency following the florid secondary eruptive period, the syphilitic infection following its natural course, or failing arrest by treatment, is quite prone to develop cutaneous lesions. At first these present the disseminate distribution and relatively nondestructive character of the secondary eruption. These we have spoken of as "recurrences" rather than as typical late lesions. As time elapses the recurrences become more solitary and more destructive, taking on the characteristics of gummatous infiltration with a combination of paucity of organisms and excessive reaction, which may be part allergy part vascular change, but which none the less has a very distinct clinical identity In the pathology of these lesions one sees the granuloma *of syphilis most typically portrayed—the giant cells, the lymphocytic infiltration*, some epithelioid and fibroblastic proliferation, peripheral obliterative endarteritis of the finer capillaries and arterioles, and central softening and necrosis. In the earlier stages of the infiltration the picture of profuse round-cell infiltration may suggest, apparently round-cell sarcoma. In the later fully developed granuloma the picture may to the inexperienced, strongly suggest tuberculosis until all the clinical evidence is at hand.

Atrophic and Pigmentary Syphilids.—The general rule that secondary syphilids involute without trace of their presence has definite exceptions in the atrophic and pigmentary residua, which are among the most distinctive lesions of the latent period of the disease, and the most helpful landmarks in the identification of infections which might never otherwise attract attention. The chief source of residual changes is the loss of pigment-producing power in certain cases of macular and maculopapular syphilids, sometimes accompanied in certain predisposed individuals, on involution, by a faint depression or macular atrophy at the site of the preceding lesion. The atrophy or the

less of the system of treatment appraisal a great deal of effect in reversing slightly abnormal spinal fluids was produced even by a small amount of treatment. On the other hand, this effect was much less striking with respect to the more markedly abnormal fluids, including those with positive serologic reactions and especially those with paretic or Type III formulae

The difference between slight abnormality and marked abnormality is especially apparent in the paretic formulae Under both systems of appraisal it is at least twice as difficult to reverse a paretic as any other markedly abnormal fluid under little or much treatment (little treatment, 30.8 per cent reversed *vs* 69.2 per cent which failed to reverse and much treatment 38.5 reversed *vs* 61.5 failed to reverse) This is true even when tryparsamide and malarial therapy results are included

Fig 445

THE DECALOGUE OF PREVENTION OF EARLY NEUROSYPHILIS

1 Never give single arsenical injections, short courses (3 to 4 injections) or mercury by mouth. Give 8 to 10 arsphenamine injections in the first course
2. No rest intervals. Have the patient on one or another effective form of treatment continuously the first year
3. Examine the spinal fluid before the end of the first year and in any case before a rest period Have the puncture correctly done, so that there will be no confusion about the cell count (no blood contamination)
4 Take slight rises in cell count (above 7) seriously especially if found after the patient has had some treatment.
5 The appearance of a paretic formula is serious. If it does not respond within eight weeks to intensification of treatment, the fluid examination being repeated, it calls for tryparsamide or fever therapy The later in the course of systematic energetic treatment that this formula occurs, the more serious it is.
6. A resistant positive blood serological test must be thought of as suggestive of early neurosyphilis, examine the spinal fluid.
7 A negative blood serological test does not make a spinal fluid examination unnecessary
8. When possible have the fundus of the eye examined early for signs of nerve involvement.
9 Signs in the fluid usually precede symptoms from the nervous system. Do not expect to detect early neurosyphilis by relying on reflex changes, abnormal pupils, etc. These are late neurosyphilis.
10 Remember that headache is significant but not conclusive and that a spinal fluid may be normal, but the patient have or later develop, neurosyphilis.

Treatment-fast spinal fluids resisting all efforts to reverse them appeared in 1.3 per cent of the total number of patients seen and 5 8 per cent of the 730 abnormal spinal fluids. This is almost identical with the incidence of paresis from the clinical side in Bruusgaard's postmortem series of spontaneously evolving untreated syphilitic patients.

It appeared finally that more irreversible spinal fluids developed among seropositive primary early secondary and delayed secondary cases than among seronegative primary cases, the per cent being 0 0 seronegative primary 1 0 seropositive primary 1.3 early secondary and 6 2 delayed secondary Thus it appears again that the institution of treatment in the seronegative primary stage has the most significant advantage of reducing the probability that the nervous system will be irremediably involved.

In Fig 445 are summarized the preventive principles applicable in early neurosyphilis. Details as to procedure are included in the chapter on Neurosyphilis.

CHAPTER XV

THE LANDMARKS OF LATE SYPHILIS ON SKIN AND MUCOUS MEMBRANES

Familiarity with the cutaneous lesions and scars of late syphilis is of great value to the diagnostician in that it serves in the first place to provide "suspicion arousers" in the case of patients whose general medical condition does not suggest syphilis, and in the second place not infrequently provides sufficient evidence to clinch the diagnosis in the absence of that almost universal criterion of reference the positive blood serologic reaction. This latter function will of course vary in importance with the serological technic employed it is only fair to say that the proportion of negative blood serologic reactions observed in the ensuing case presentations is probably higher than we would now obtain with the Kolmer technic or other sensitive procedure. But the fact remains that the first, the chief or the only clue to a latent syphilitic infection or rather a relatively quiescent one, may be in some lesion of skin or mucosae to which the patient has given little or no attention, and that a cutaneous or mucosal lesion, correctly interpreted, may identify a syphilitic infection which would otherwise be missed because of anomalous signs or a negative serology

In the period of latency following the florid secondary eruptive period, the syphilitic infection following its natural course, or failing arrest by treatment, is quite prone to develop cutaneous lesions. At first these present the disseminate distribution and relatively nondestructive character of the secondary eruption. These we have spoken of as "recurrences" rather than as typical late lesions. As time elapses the recurrences become more solitary and more destructive, taking on the characteristics of gummatous infiltration, with a combination of paucity of organisms and excessive reaction, which may be part allergy part vascular change, but which none the less has a very distinct clinical identity In the pathology of these lesions one sees the granuloma of syphilis most typically portrayed—the giant cells, the lymphocytic infiltration, some epithelioid and fibroblastic proliferation, peripheral obliterative endarteritis of the finer capillaries and arterioles, and central softening and necrosis. In the earlier stages of the infiltration the picture of profuse round cell infiltration may suggest, apparently round-cell sarcoma. In the later fully developed granuloma the picture may to the inexperienced strongly suggest tuberculosis until all the clinical evidence is at hand.

Atrophic and Pigmentary Syphilids.—The general rule that secondary syphilids involute without trace of their presence has definite exceptions in the atrophic and pigmentary residua, which are among the most distinctive lesions of the latent period of the disease, and the most helpful landmarks in the identification of infections which might never otherwise attract attention. The chief source of residual changes is the loss of pigment-producing power in certain cases of macular and maculopapular syphilids, sometimes accompanied in certain predisposed individuals, on involution, by a faint depression or macular atrophy at the site of the preceding lesion The atrophy or the

depigmentation may appear separately and without the necessary intervention of a previous visible syphilid The favorite site for the macular depigmen



FIG. 446 —SUSPECT PIEBALD NECK.

The history of this patient, who presents typical leukoderma colli, illustrates number of interesting diagnostic points. He entered the clinic in a state of stupor and disorientation bordering on coma. According to his escort he came for failing vision, of sudden onset, with diplopia. An xtreme grade of ataxia had developed in two days time. A genital scar was present, but no history of infection was obtainable. A year before entry h had had "smallpox. A superficial trophic scarring, shown in Fig. 402, bore testimony t the fact that his secondary syphilid had been diagnosed variola.

On examination it was found that the patient had left homonymous hemianopsia, an acut recent paralysis of the left internal rectus, positive blood Wassermann reaction, and neurological signs of a rapidly progressive meningeal and vascular process in the nervous system hich "looks like CNS lues. The positive Wassermann reaction sent him to the syphilologist, who then identified the pathognomonic sign of leukoderma colli, and identified the supposed variola scarring as the atrophic macula syphiloderm. The macular atrophy is not true scar of the varioliform type It is rather thinning of the skin without marked change in the appendages, and show itself quit as often by bulging t the site of the atrophic macula as by depression. It cannot be denied, however that the scarring of variola and the macular atrophy of syphilis may t times closely resemble each other I this case the slow course of the smallpox, the purely macular and papular character of the lesions, and the absence of the distinctive variola prodromes and sequelae of a constitutional type might have suggested the correct diagnosis in patient with so profuse an eruption.

Neurologically speaking, this patient presents the encephalomyelitis of early syphilis of the nervous system The process is apparently primary and not neurorecurrence due to inadequate treatment. While the response of the patient to treatment was good, he never entirely recovered normal mentality the so-called psychic scar of Collins persisting (see Chapter XX). The spinal fluid t entrance showed the following findings

WR /// 0.5 and 0.4 cc., Nonne positive 80 lymphocytes.

The earlier recognition of the pigmentary syphiloderm or the papular secondaries might have forestalled so serious process in the nervous system.

tation is the side of the neck the macular atrophy occurring on the back and flanks

Syphilitic Leukoderma.—"Syphilitic leukoderma" as the pigmentary disturbance is called or "leukoderma colli" when the changes occur as they

most frequently do upon the neck and shoulders, is a highly characteristic lesion, with almost pathognomonic value in diagnosis. The best imitation of it is said to be produced by the pigmentation accompanying the *involution* of an extensive psoriasis under arsenical medication. This is, in our experience, rarely confusing. Chloasma, the patchy hyperpigmentation of the forehead, face, and neck about the ears, in women with asthenia and uterine disturbances, does not show the definite macular character or "spotting" of true



FIG. 417.—SYPHILITIC LEUKODERMA FOLLOWING INVOLUTION OF A SYPHILID UNDER TREATMENT.

This is an example of syphilitic leukoderma considerably more extensive than mere leukoderma colli. It developed during the involution under treatment of maculopapular syphilid, associated with mucous patches and condylomata. The macular depigmentation on more or less general hyperpigmentation extends to the shoulders, back, and arms. Over the lower thorax and lumbar regions the macular depigmentation passes over into the atrophic macular syphiloderm. In extensive syphilitic leukoderma one should bear in mind the differentiation from vitiligo, patchy depigmentation with slight marginal hyperpigmentation involving large areas, having more or less of geographic contour rather than the appearance of smaller scattered macules upon darker background.

The history of this case presents several points of interest from the standpoint of diagnosis.

The patient was married, thirty-three years of age, her husband salesman. Two months before entry into the clinic she had had an "ulceration" involving the labia, which was painful, not associated with lymph node inflammation, and cleared up in two weeks. She did not see physician at this time. As the labial lesions cleared up, an eruption began t appear on the neck, which extended to the entire body with the exception of the scalp, palms, and soles.

When the eruption first appeared she stated that she visited physician who told her it would soon pass off. No further inquiries were made, apparently.

One week before coming to the clinic she visited physician in neighboring large city who took blood test, told her the result was negative, and gave her white lotion.

The patient was positive that neither physician had inquired about the genital lesion, nor had either examined her mouth, or in fact, given the condition more than casual inspection.

A darkfield examination of mucous patches about the labia when she entered the clinic showed *Spirochaeta pallida*. The Wassermann reaction was also positive.

syphilitic leukoderma, but is a vague, irregular patchy semigeographic affair of fawns and browns, a discoloration rather than a white spotting with definite oval depigmented macules. Vitiligo, the depigmentation in large geographic areas, whose cause is entirely unknown, need not be a source of confusion. The geographic contours and large individual depigmented areas are entirely different from the close-set but discrete macular depigmentation of syphilitic leukoderma. The question as to whether vitiligo or better leukoderma m

general can be regarded as frequently of syphilitic origin has been considered by a number of authors, whose opinions, with observations of his own, are *summarized by John Lane. Unless the term "leukoderma" is used in the* French sense, to include syphilitic pigmentary changes, the instrumentality of syphilis seems to be small The use of the term vitiligo for the general condition will assist in preventing confusion. The erythema from hot or cold applications produces a type of retiform coarsely meshed pigmentation (Fig. 448) whose history will usually distinguish it, and which lacks the definite macular lesions that may usually be found in a true syphilitic leukoderma. The Juliusberg type of parapsoriasis sometimes produces a pigmentary change (Fig 295) quite suggestive of syphilitic leukoderma, which we have known to deceive careful observers momentarily but which rarely confuses on further study of the eruption as a whole.

Ehrmann and Wertheim have proposed the most recent theory of the origin of syphilitic leukoderma in the form of functional inhibition of the pig



Fig. 448 —Retiform pigmentation of the neck caused by the application of heat t swollen glands. The history of repeated or protracted hot or cold applications usually eliminates this condition from differential diagnosis Note the coarseness of the mottling which is entirely different from the macular depigmentation of syphilitic leukoderma.

ment cells of the basal layer of the epidermis within the macular or papular lesion produced by the presence of *Spirochaeta pallida* They find that leukoderma is present in abortive form in most patients with macular and papular syphilids, but that the leukoderma of the syphilitic lesion is only brought out by the exposure of the rest of the skin to light with resultant contrasting hyperpigmentation The functional disability disappears after a time permitting the restoration of the skin to normal The occurrence of a leukoderma during involution under treatment without special exposure to light, however seems to argue that there are other factors besides light, including a possible hyperpigmentation due to arsenic in some cases The combination of hyperpigmentation, depigmented macules, and macular atrophy is well shown in Fig 447

Recurrent and Late Syphilids of the Skin.—Didactic teaching of the morphology and diagnosis of late syphilids by laying too much emphasis upon mere names and upon disparateness rather than fundamental unity has, we

Fig. 449.

THE TEN BASIC PHYSICAL CHARACTERISTICS OF LATE SYPHILIDS

1. Solitary character; or at least the presence of few lesions.
2. Asymmetry; though by no means invariable.
3. Induration: deep palpable infiltration.
4. Indolence; relatively low-grade inflammatory process.
5. Arciform configuration; borders polycyclic or forming segments of circles, both in the individual lesion and in the configuration of a group of lesions.
6. Sharp margination of lesions; in ulcers, "punched out" appearance.
7. Tissue destruction and replacement with or without ulceration.
8. Tendency to central or one-sided healing with peripheral extension.
9. Scar formation; superficial *atrophic* (thin and wrinkled) *non-contractile*. The scar retains the arciform configuration of the original lesion.
10. Peripheral hyperpigmentation of a rather persistent type.



FIG. 450.—THE "SHOWER" OF NODULAR LATE RECURRENCES.

This lesion might be designated figuratively as a "shower" of recurrences. The scar produced by such a lesion is shown in Fig. 468. All the essential characteristics of a late syphilid are present except the arciform configuration. After the involution of such a lesion and, in fact, during its activity differentiation from a papulonecrotic tuberculid and from the scars of acne necrotica might be necessary. The zigzag lines of pigmentation, which show that some of the individual lesions have "traveled," eliminate the two possibilities mentioned.

This infection was of four years' duration and began with a chancre in the vagina. At the time of examination the lesion pictured was of one year's duration, and the chest, upper arms, and chin were involved. This lesion partakes to some extent then of the wide distribution of a secondary lesion with the physical characteristics of a late syphilid.

believe, befogged the relatively simple essentials of diagnosis in a cloud of nomenclature. We shall accordingly not discuss the nomenclature of various



Fig 451 —This is typical annular papular recurrence during the course of an otherwise practically quiescent syphilitic infection. Note the arciform and polycyclic grouping of papules in the upper lesion and the scalloped contour of the lower The faint pigmentation of the center is also pparent. The border is faint brownish-pink color and definitely though not deeply indurated Lesions of this type may be much more profuse and widely scattered.

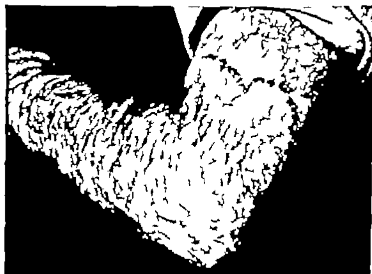


Fig. 452 —This is typical psoriasiform circinate papular recurrent syphilid in patient with syphilitic aortitis and positive blood Wassermann reaction. Note the faint pigmentation toward the convex side of the lesion which indicates the direction of extension as being up the arm. The extensor surface of the forearm, which presents lesions somewhat resembling tubercalid in appearance is show in Fig. 543 The arciform configuration is the main clinching point in the morphological diagnosis of the syphilid.

types of late syphilids beyond the division into nodular nonulcerative forms, nodulo-ulcerative types, and simple gumma. The nodular types are gummatous infiltrations which do not break down. Involution, while it may occur without leaving a trace, is usually accompanied by some degree of atrophy and pigmentation. There may or may not be slight scaling and what appears to be scale may at times be found on closer examination to be crusting over



FIG. 453.—THE PSORIASIFORM LATE SYPHILID.

Late syphilids may be of extreme superficiality and atypical configuration and leave so little in the way of scarring and atrophy that the objective diagnosis from the lesion may be momentarily in doubt, or have to depend on collateral evidence. This is especially the case in what might be called the psoriasiform late syphilid, of which Fig. 453 is an example. A vital element in the differentiation is the search for the slightest sign of erosion or ulceration, and in the careful distinguishing of *crust* from *scale*. At several points in the large irregular patches the dark brownish points of crusting are visible, and removal of these crusts discloses superficial but definite erosions, not the smooth shiny bright red surface of the scaling psoriatic papule. Compare the scale and structure of the psoriatic lesions in Fig. 455. The syphilid was so superficial that it had produced almost no atrophy, but the residual pigmentation in the areas over which the infiltration has wandered is very apparent. Residual pigmentation may occur in psoriasis, but it is usually the result of treatment, especially with chrysarobin, arsenic, or the *roentgen-ray, and is not so sharply defined.*

In history and diagnosis this case presented no distinctive features. The Wassermann reaction was positive, the infection of perhaps thirteen years' duration. The psoriasiform lesions were unusually extensive, involving most of the trunk and legs. The differential diagnosis of psoriasis and syphilis is further discussed in Figs. 454, 456, 457.

a superficial ulcer. Nodulo-ulcerative types may present both nodular lesions and ulcerative breakdown in varying proportions. The infiltrative phase may be shortlived and inconspicuous, and the ulcerative lesions multiple and relatively deep. The configuration both of this type and the preceding is extremely important, and as much attention should be paid by the examiner to the gross appearance and "picture" of the lesion as to its individual units.



Fig 431 —This is typical annular papular recurrence during the course of an otherwise practically quiescent syphilitic infection. Not the arciform and polycyclic grouping of papules in the upper lesion and the scalloped contour of the lower The f int pigmentation of the center is also pparent. The border is faint brownish-pink color and definitely though not deeply indurated. Lesions of this type may be much more profuse and widely scattered.

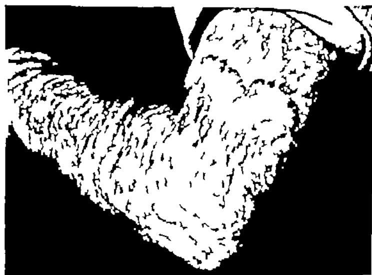


Fig 432 —This i typical psoriasiform circinat papular recurrent syphilid in patient with syphilitic aortitis and positive blood W ssermann reaction. Not the faint pigmentation toward the convex side of the lesion which indicates the direction of extension as being up the arm. The extensor surface of the forearm hich presents lesions somewhat resembling tuberculid in ppearance is show in Fig 543 The arciform configuration is the main clinching point in the morphological diagnosis of the syphilid



Fig 435.—Psoriasis of the back for comparison with Figs. 433 and 437

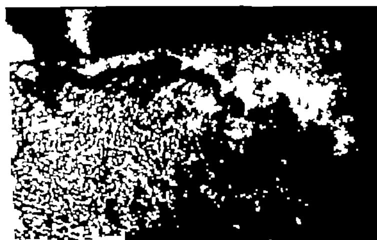


Fig. 436.—This figure is introduced at this point for contrast with Fig. 437 Note the difference between the two types of border While both are arciform, that of the syphilid (Fig 437) is the more pronounced and the more coarsely nodular The border of the above lesion is composed of miliary nodules. Note too the persistence of activity in the center The lesion shown above is tuberculous, and the miliary nodules are individual tubercles. The persistence of the process in the scar is more distinctive of tuberculosis. The differential diagnosis of tuberculosis and late syphilis of the skin is discussed further in Figs. 473, 480.

the actual arciform lesion. He reasoned by analogy that the allergic, or *Umstimmung* type of tissue reaction in late syphilis would make it possible for relatively small number of organisms to produce particularly choice and well delineated examples of this immunobiologic reaction resulting in circinate and arciform configuration.

In fact, it is precisely because he fails to see the shape and arrangement of the parts of a late syphilid that the average observer makes mistakes. He pays too much attention to the fact of nodulation or crusting or ulceration, and does not notice the pathognomonic geography of the process. Scar formation, always highly significant and always demanding explanation, often escapes undetected in the interest aroused by the active part of the process. The solitary "gumma," a relatively less important lesion of late syphilis, has



FIG. 457.—A TYPICAL CIRCINATE NODULAR LATE SYPHILID.

The bearer of this gaboard was wholly unaware that anything ailed his back. He came for intermittent stomach trouble of five years' duration, which on the completion of his medical examination proved to be due to a duodenal ulcer.

This eruption occurs upon the seborrheic area of the back, and should be compared with Fig. 480 (seborrhea petaloides) to assist in differentiation, and also with Fig. 455 (psoriasis). The essential lesion was a pink *indurated* papule with a marked tendency to brownish pigmentation. Some of the circinate groupings were slightly scaling, but there was no suggestion of the abundant imbricated silvery scale of psoriasis. The lesions left scars, superficial, atrophic, and preserving a record of the configuration of the involuted lesions.

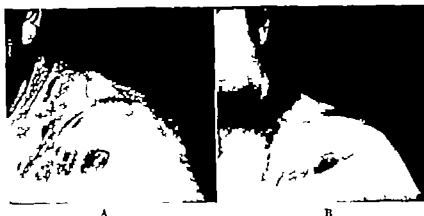
Compare the coarsely papular or nodular border with that in Fig. 456.

Any one of these indurated, arciform, nodular, scar-producing lesions would have made a 90 per cent diagnosis of syphilis, regardless of the Wassermann reaction. The patient had had gonorrhea seventeen years before but could give no history of syphilis. He was seen before organized work in the Section of Dermatology was begun and further records are incomplete. The response to treatment was prompt.

The indurated arc with scars does not need ulceration to arouse the strongest suspicions of syphilis.

received most of the emphasis in teaching in the past, and is the average practitioner's conception of a late syphilid. It develops as a cutaneous or subcutaneous tumor, at first pinkish, then becoming rapidly a darker red to bluish tinge. General softening occurs or a minute punctum may form at the highest point, whose rapidly extending margin permits a discharge of grumous pus, or more often discloses a yellowish tough rubbery slough which on final separation leaves a granulating ulcer. The gumma may occasionally involute

without breaking down. These three types, then the papular or nodular the nodulo-ulcerative, and the simple gumma, are the distinctive groups of late cutaneous syphilids.



A B

Fig 438.—A classical syphilid of the nodulo-ulcerative type. The lesion was of years' duration and had been treated locally Note how much more apparent the base morphological features are hen the lesion begins to clean up and heal. The lack of definition in the earlier photograph is due to eczematous changes from local treatment.

This patient had had 12 pregnancies, one miscarriage, nd three stillbirths without the fact arousing suspicion enough t lead to Wassermann test at the time she sustained an operation in 1913.



Fig. 439.—A typical ery superficial nodulo-ulcerative syphilid of the neck. The patient could give no history of syphilis, but had had gonorrhea nine years before. The tongue showed sclerosing glossitis (see Fig. 524) The Wassermann reaction as positive. This patient came to the clinic for duodenal ulcer syndrome and had no notion that he had syphilis.

The Basic Physical Characteristics of Late Cutaneous Syphilids.—Figure 440 summarizes the physical characteristics of the late syphilid. No one of the ten individual items can be accepted alone, but the combinations often achieve pathognomonic value and quite outrank the blood serologic test in their diagnostic worth All granulomatous processes in the skin share some of these

characteristics in varying degree. In the diagnosis of syphilids the combination of induration with arciform or polycyclic configuration is perhaps the most



Fig 460 —The solitary gumma is the classical late or tertiary syphilid of the older medical texts and teaching, and the only one which arouses the suspicions of many physicians. It is a comparatively uncommon lesion, which begins as a small nodule, often at site of trauma, especially over the bones of the skull, the presternal, the supraclavicular and the pretibial regions. This nodule grows t tumor of variable size, which has rubbery elastic feel and often dusky color In this condition it is often taken for a malignant neoplasm or tuberculosis (see Figs. 434, 478) nd cut into for diagnosis, or excised outright. This clinical diagnosis of malignant neoplasm is at times apparently confirmed by a report of round-cell sarcoma from the pathologic laboratory Especially is such diagnosis apt to be made if the lesion is young Older gummata show such marked inflammatory changes and fibrosis that they are recognized as granulomata. The danger is that if they contain giant cells, as they well may the inexperienced will regard them as tuberculous.

Both the appearance of this ulcer and its location over the claviculo-acromial articulation at once suggest syphilis. The findings and history in this case presented the following outstanding points in diagnosis.

1 The patient s shoulder lesion was not her chief complaint. She came for soreness at the base of the tongue and in the throat following extraction of tooth year before. The patient and her physician had both recognized that these lesions were ulcers, but she had received only gargles and mouth-washes, and teaspoonful of some liquid medicine of unknown type three times daily for three months.

2. She had had one miscarriage 2 children had died in infancy and she had 2 living healthy children. She recalled that her husband had taken rubbing treatment before marriage, thirteen years ago.

3. Her first Wassermann reaction in the clinic was egative

4. Three subsequent tests ere positive

5. The spinal fluid was negative.

6. The living children showed no evidence of the disease. The father would not report for examination.

7 The patient disappeared from observation and t eatment after her third arsphenamine injection.

8. Th shoulder lesion in this patient was regarded carbuncle.

"Small round-cell sarcoma, tuberculosis, and bscess" or carbuncle" are the masquerades in diagnosis of more than one gumma.

important, and the trained palpating finger is repeatedly called into use by the expert in differentiating such lesions. An indurated arc or circle or an arci-

form or scalloped chain of fleshy papules should arouse the most insistent suspicion. Similarly the arciform grouping of ulcers and scallops or arcs in



FIG. 461 —THE TYPICAL NODULO-ULCERATIVE SYPHILID—WASSERMANN NEGATIVE.

This lesion is the ideal nodulo-ulcerative late syphilid. It presents every single one of the ten fundamental characteristics. It is the only lesion on the body (speaking of the group of ulcers as the "lesion") It is unilateral, indurated, indolent. Note that the surrounding skin in the direction of extension is practically normal. There is no suggestion of metastatic nodule formation beyond the periphery as in lupus vulgaris, no diffuse inflammatory areola, as in ecthymatous processes. The arc is perfect, the margin sharply defined, the lesion obviously destructive. Healing has been central, the lesion spreading fan-shaped toward the periphery The non-contractile character of the scar is evidenced by the absolute lack of distortion of face over which an ulcerative lesion of such area and depth has passed. Even the crows feet at the outer canthus of the eye are absolutely unaltered by tension. The hyperpigmentation of the periphery of the scar is less apparent than in some syphilids, but can be recognized along the healed margin. The lesion had begun as nodule ten months before the patient came to the clinic.

When the lesion was three months old the patient had consulted physician, but had been lost track of He had had his suspicions aroused and had had Wassermann reaction taken, which was negative. The patient then disappeared from observation, and when seen again the lesion had reached its present size and configuration. A diagnosis of *lupus vulgaris* had been made, and she had received one roentgen-ray treatment, without any effect on the lesion.

It is evident that the negative Wassermann reaction had eliminated syphilis in the mind of the physician who first saw this case and who subsequently made diagnosis of lupus vulgaris (tuberculosis cutis) The correctness of the negative Wassermann result was confirmed by our own findings. This patient has never had positiv Wassermann reaction on th blood in more than two years' observation. Her spinal fluid is negative. There is no evidence of syphilis in any of the viscera or special sense organs, and the neurologic examination is negative. The only point in her history suggestive of syphilis is the occurrence of four miscarriages following the birth of four living healthy children.

A positive Wassermann reaction is in no way necessary to the diagnosis of syphilis from lesion such as this, although it would be valuable confirmation. Aside from the fact that it is perfect syphilid, the diagnosis of lupus vulgaris is eliminated by the absence of tubercles (" apple-jelly" nodules) by the rapid course, the non-contractile scar and the immediate and complete response to arsphenamine and inunctions.

the margin of thin atrophic scars should receive the most careful consideration and checking. The noncontractile scar of the superficial late syphilid while imitated at times by such processes as the dry erythematous type of tuber

culous and the scars of the tuberculous lesion known as erythema induratum (Fig 556) is none the less an important and distinctive feature. It is remark

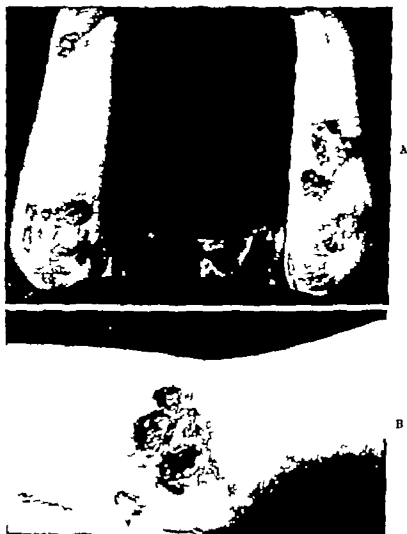


FIG. 462.—ACCORDING TO THE PATIENT'S STATEMENT PHYSICIANS LOOKED AT THE CONDITION SHOWN IN A AND CURED WITH VACCINE, APPARENTLY UNDER THE IMPRESSION THAT IT WAS EITHER FURUNCULOSIS OR ECTHYMA. HAD HE SEARCHED FOR THE YOUNGEST LESION SHOWN IN B, HE WOULD HAVE ENCOUNTERED A TYPICAL PICTURE OF THE ULCERATIVE LATE SYPHILID WITH ALL THE ESSENTIAL CHARACTERISTICS FOR A DIAGNOSIS.

The clover-leaf configuration produces the polycyclic border; the process extends peripherally as it heals centrally; there is distinct pigmentation along the involuted edge; the scar is not sufficiently large as yet to show all the orthodox characteristics. The ulcers have a typical punched-out appearance. *The characteristics of the scar are better seen in the ulceration on the extensor surface shown in A.*

The Wassermann reaction was strongly positive. It had apparently never been taken prior to her entry into the clinic.

able how even a deeply ulcerative syphilid may wander about the face (Figs. 500, 501) invading even the eyelid without producing ectropion, while a more

remote tuberculous ulcerative process (Fig. 494 B) may evert the lid and even distort the mouth and lips. The scar of blastomycosis presents a similar and diagnostically important tendency to contracture (Fig 505) The periph



FIG. 483.—THESE TWO PHOTOGRAPHS ARE SHOWN TOGETHER TO ILLUSTRATE THE MEANING OF THE TERM "CONFIGURATION" AS APPLIED TO THE MARGIN OF ULCERS RATHER THAN TO GROUP OF LESIONS.

The upper ulcer has the arciform or polycyclic configuration characteristic of syphilitic gummatous ulcer. The lower is irregular with jagged margin, undermined at certain points, crusted and ecthymatous at others, and with gangrenous remnants of tissue about the base. Ulcers of this type may result from local bacterial invasion (as in diabetes) or hematogenous dissemination of pyogenic organisms. The process may at times be tuberculous in character (approaching the type of erythema induratum) It is important t remember that ulcerative processes about the long bones may produce local osteoperiostitis or be the sequels of involvement of the bone, so that the mere finding of periostitis by roentgen-ray in conjunction with an ulcer over bone is not proof that the process is syphilitic.

The history of the patient with the gummatous ulcer illustrates the way in which modern treatment methods, improperly carried out, are altering the clinical landmarks of syphilis. (See Chapters I and XIV)

eral hyperpigmentation of the late syphilid may be simulated at times by the effect of vascular stasis in chronic ulcers of the lower extremity but the pigmentation of vascular stasis tends to be diffuse and extensive, the typical pigmentation of the syphilid to be limited to the margin of the scar forming

a narrow band. Tuberculids of the leg (erythema induratum) may show this marginal pigmentation of their scars, but the scars of other granulomatous



FIG. 464.—THE SITUATION OF ULCERS ON THE LOWER EXTREMITIES HAS OCCASIONALLY CONSIDERABLE SUGGESTIVE VALUE IN DIAGNOSIS.

No invariable rule exists, but the following rules of thumb are helpful

1 Ulcers over the upper two-thirds, especially of the anterior and outer aspects of the tibia, are more apt to be syphilitic than ulcers of the inner lower third.

2. Ulcers of the lower third of the leg, especially of the inner aspect, usually involve a circulatory stasis factor and are more apt to be varicose than syphilitic, or to have the one process imposed on the other

3. Ulcers of the calf region, especially in women, are more suggestive of tuberculosis (erythema induratum) than syphilis, though both may be present.

A sharp or punched-out margin and circular outline do not prove a leg ulcer to be syphilitic, especially in the presence of evidence of vascular stasis.

The typical stasis or anemic ulcer is usually of long standing and surrounded by a dense ring or considerable area of scar tissue and inelastic hide-bound and thickened or glazed skin. The border is sharply defined, rounded, not much elevated, and the base is flat and covered with small pale granulations. The fibrous proliferation about the ulcer often binds it tight to the deeper connective tissue over the bone. There may be associated periosteal changes. Look for varicose veins, old eczematous changes, and elephantiasic thickening of the skin with hyperpigmentation around the ankle as a guide to a stasis factor in ulcers of the leg

The ulcer shown in this illustration is an anemic ulcer occurring in a patient with syphilis, complicated by a compound fracture with secondary infection, periostitis of the fibula, and arthritis of the metatarsal articulations. The situation of the ulcer, its flat anemic base and hide-bound border surrounded by a general fibrosis and hyperpigmentation, are characteristic of a traumatic-stasis ulcer. While the osteoperiostitis responded to a considerable extent to antisyphilitic treatment, the ulcer as such began to heal only when measures to combat the vascular stasis (gelatin stocking) were undertaken.

Kilbourne has advised bismuth and iodide therapeutic test in leg ulcers suggestive of syphilis in seronegative patients, in preference to the arsphenamines.

lesions are singularly free from it. The peripheral pigmentation of a syphilid has a remarkable persistence, and may remain unchanged for months or fade slowly over several years



Fig. 403.—This is a late syphilid in a location more in keeping with inguinal granuloma and phagedenic chancroid. The epithelioma-like border of the larger ulcer might be confusing were it not for the evidence of extensive healing, the multiplicity of the lesions, and the type of scar. A similar type of lesion on the face is shown in Fig. 800. The blood Wassermann reaction must often be the differentiating factor between this lesion and the chronic phagedenic chancroid, which latter, however, is much more destructive.



Fig. 404.—The typical atrophic scar of an arciform nodular or infiltrative syphilid. Note the patulous follicle mouths and the faint atrophic crinkling. This patient had an asymptomatic neurosyphilis with a negative blood Wassermann reaction. There were other scars on the body which attracted attention to the underlying syphilis. His chief complaint was nervousness.



Fig 467 —These t scars were the result pparently of syphilitic lesions in man approaching sixty years of age which had been healed with axle grease. Note the lobulation and the marked peripheral hyperpigmentation in A (tattoo?) Note also the trophic wrinkling. The scar in B shows the punching or stencilling that suggests syphilitic origin.

The Wassermann reaction was strongly positive. This finding the cutaneous scars, and penile scar were so far as could be ascertained from the most searching examination of every accessible structure of the body bsolutely th only bjective manifestations of syphilis which was apparently contracted in 1886, t hich time he had a chancroid that was treated locally *H had never received any treatment for syphilis.*



Fig. 468.—The cluster of small round trophic scars on the front of this patient thorax are those of typical shower of recurrences such as show in act ve form in Fig. 450. This patient had other scars on the back and thighs hich ere typical of the arciform nodulo-ulcerative syphilid.

The blood Wassermann reaction and th spinal fluid were gative epeatedly The patient had definit history of syphilitic infection contracted t enty-t years before.



Fig 460 —This patient illustrates the importance of the combination of active lesion and scar in the diagnosis of cutaneous syphilids. The patient, aged forty married, had complained of stiff shoulder. The trouble had come on following fall in hich he had fractured his clavicle on the affected side. Good union had occurred, but stiffness of the shoulder followed.

In the course of his examination doubtful history of syphilis was elicited. His knee-jerks are reduced. The patient's blood was seronegative. Roentgenograms of shoulder and teeth were negative. The patient had had stiff spine for sixteen years. The right testicle contained firm nodule. Manipulation of the shoulder under ether was ordered and performed, ith temporary benefit.

At the time of this examination the lesions shown above were described as "areas of chronic irritation on both forearms, and the patient stated later that he had been told they were cuff chafes. Dermatologic consultation was not called.

Six months later patient was re-examined on complaint of pain in the side. At this time prostatitis was recognized. The Wassermann reaction was again negative, but dermatologic consultation as called. The lesions were of about year standing t the time of the photograph.

What is there about these lesions that should arouse suspicion?

1. They are destructive. Actual ulcers exist below the crusts.

2. They produce scars, whose configuration is circinate, which are trophic and noncontractile, and peripherally hyperpigmented.

3. The active lesions are indurated.

The provocative Wassermann reaction yielded two strong positives and two weak positives in seven tests. There was also an immediate flare-up (Herxheimer) and subsidence of the lesions

The aches and pains disappeared promptly under treatment, but there was no resolution of the old process in the spine. The shoulders, however which were still causing some trouble, cleared up entirely Certain paresthesias about the thorax and waist were attributed by the neurologists as much t the spondylitis as to the possibility of neurosyphilis. There were definite lightning pains in the legs, however

A high index of suspicion demands satisfactory explanation and an elimination of syphilis in scar-producing lesions of th skin.

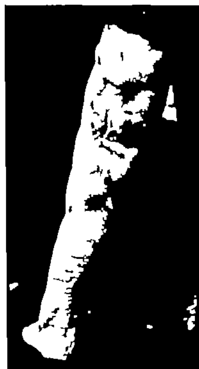


Fig 470—An exception t the relatively superficial and non-contractile character of the scars of the cutaneous syphilids. This is the scar of the deep gumma, which entails usually an enormous destruction of tissue and leaves correspondingly large and deforming scar not unlike that of solitary gumma of the liver

Thirty-seven years ago this woman, now sixty-one years of age, developed ulcers over the left tibia which healed spontaneously Seventeen years later contracture developed hich it appears by examination t this time was due to peripheral nerve injury Six years ago abscesses began to develop about the knee and in the flesh of the left thigh posteriorly The lesions ere lanced repeatedly and refused to heal, forming sinuses which drained for months t time. On one occasion curetment of one of the sinuses was performed She also sustained tendon transplant for the shortening that occurred in conjunction with the paralysis. At this time she had ulcers on the front of the knee. The family history was not in the least suggestive of syphilis and her personal history on this score was negative.

This type of deep destructive scarring with chronic sinus formation may of course, be tuberculous and even pyogenic the sequel of chronic suppurative osteomyelitis. But the significant fact in this case is that no ttempt was apparently made through period of six years to reach satisfactory diagnosis When the patient entered the clinic she had never had Wassermann test or roentgenographic study of the bony structures involved

The Wassermann reaction was strongly positive

The radiogram of the left knee and leg showed periosteal changes suggestive of syphilis.

This patient had evidence of syphilis that should have identified her case without the positive Wassermann reaction. Her pupils were of th Argyll R bertson type, her Romberg was positive; there were slight reflex changes.

It is interesting t note that one inexperienced examiner called the leg lesions "trophic.

GENERAL DIFFERENTIATION OF LATE CUTANEOUS SYPHILIS FROM OTHER GRANULOMAS OF THE SKIN

The differentiation of late syphilids from tuberculosis, lepra, sporotrichosis, blastomycosis, and vegetative granuloma must be a routine part of the business of every physician who deals with syphilis. The differentiation should not be made on the basis of the blood serologic reaction alone nor is it always

possible to invoke other systemic signs of syphilis or tuberculosis to assist in a differentiation of these two diseases. The decision must, therefore be made at times on morphological considerations and direct laboratory investigation of the lesion alone, or in such a study must be found the crucial evidence to clinch a diagnosis suggested but not confirmed by other signs. The aspect of this differential problem changes with every case. It is impossible to draw up a tabular statement which applies equally to lesions situated upon the face and upon the leg The constitutional accompaniments, instead of shedding light, may increase confusion. Even the therapeutic test has serious pitfalls,



Fig. 471.—An illustration of the importance of location as well as configuration in determining the character of scar This patient had been treated for several months on diagnosis of "varicose ulcer though there were no apparent varicosities, and the lesion is high and oddly situated for an ulcer with stasis factor T be typically varicose there should be varicosities, deep or superficial; edema; and the ulcer would be more likely to appear on the inner aspect *of the leg near the ankle*, upon a skin showing t least some evidence of chronic vascular change, inflammation, and thickening, instead of the entire normality apparent in the figure. Note the sharp circumscription of the pigment. This patient also had an asymptomatic neurosyphilis.

and may give false positive results. It is impossible in studying the various cutaneous granulomata to escape the belief that there are certain fundamentals of bodily reaction to all the granuloma-producing agents which are present alike in syphilis, lepra, tuberculosis, sporothrix, and blastomycotic infections. The choicest picture of plasma-cell infiltration in our possession occurs not in a syphilid, where orthodoxy demands, but in a pyogenic granuloma developing upon a syringo-adenomatous nevus. It is essential to realize, therefore, that holes will be found in any scheme of differentiation of the granulomas that diagnosis must be made by preponderance of evidence and that absolutely pathognomonic signs will be few if indeed they exist at all. This caution

should be applied by the clinician who emphasizes configuration and apple-jelly nodules, by the pathologist who leans on giant cells, plasma cells, and lymphocytes and by the practitioner who depends upon the blood serologic reaction

Differentiation of Cutaneous Tuberculosis and Syphilis.—The differentiation of tuberculosis and late syphilis of the skin and mucous membranes is easily the most difficult of the series from the purely morphological standpoint. No table of differential points can completely cover the individual case or



Fig 472.—This is the typical scar of large nodulo-ulcerative syphilid of the pretibial region below the knee Not the atrophic wrinkling, the peculiar pigmentary mottling, the hyperpigmented border and the "kidney-shaped" outline There is bsolutely no distortion in spit of the large area covered by the destructive process. W have seen dozen such scars in patient whose herniotomy ound refused t heal, hich had been completely overlooked in his pre-operative examination. When after forty days in bed it became apparent that the wound was not going to heal, W ssermann reaction was taken and found strongly positive The ound promptly healed after treatment as begun.

provide infallible criteria but the following (Fig 473) will serve to summarize those particulars in which a preponderance of evidence for or against the diagnosis of tuberculosis or syphilis may be accumulated

Omitting from consideration for the moment the forms of tuberculosis previously spoken of as tuberculids, Fig. 480 p 701 presents the points which may fail to differentiate the two diseases if they are too implicitly relied upon.

The technic of recognizing the apple-jelly nodule is illustrated in Fig 4 4 This elementary lesion upon whose identification the diagnosis will often depend, is a tubercle in the deeper layers of the corium or the fat, which is

Fig. 473.

DIFFERENTIATION OF CUTANEOUS AND MUCOSAL TUBERCULOSIS AND SYPHILIS

Syphilis	*Tuberculosis.*
Polymorphism Gre ter variety of lesions in the course of the infection.	Tendency t single type of lesion throughout the course of the disease.
Tends t shorter duration and more rapid evolution of lesions (eeks or months)	Extreme chronicity of lesion (years) suggest tuberculosis.
Arciform configurations the rule.	Arciform configurations unusual.
Lesions markedly indurated (dry or nodular type)	Induration less striking
Ulceration peripheral.	Ulceration tends t be central.
Spontaneous healing not unusual	Spontaneous healing rare.
Scars usually thin, trophic non-contractile	Scars may be either trophic or tough and contractile.
Scars usually clea completely healed.	Scars pt t contain tubercles.
Peripheral pigmentation pronounced.	Peripheral pigmentation rare.
Pathologic picture of granuloma ith giant cells often not distinctive. Coat-sleeve perivascular plasma cell infiltration and obliterative endarteritis of capillaries most important. *Spirocheta pallida* present if staining technic is adequat and valiable.	Typical tubercles should be present for diagnosis. Finding of bacilli in tissue desirable in doubtful cases but usually difficult. May be present in pus from deeper lesions
Guinea-pig inoculation of tissue negativ for tuberculosis.	Guinea-pig inoculation may be positive for tuberculosis, but not invariably
Tuberculin subcutaneously 0.25 to 1 mg. produces no local reaction in lesion.	Tuberculin subcutaneously 0.25 mg., may produce definite focal and general reaction.
Wassermann reaction usually positive, but may be negative repeatedly	Wassermann reaction usually negative, but may be weakly positive.
Arsphenamin usually produces marked Herxheimer reaction.	Arsphenamin may produce slight flare-up, but not usually
Arsphenamin treatment gives complete specific response.	Arsphenamin treatment produces improvement but rarely cure.
Mercury gives the nearest to specific therapeutic test (succinimid or inunctions)	Mercury may produce slight but temporary improvement in all but mixed lesions. Bismuth action unsettled
Collateral indubitable evidence of systemic syphilis may be present.	Collateral indubitable evidence of systemic tuberculosis may be present.
Repeated absence of tubercle bacilli in sputum or secretions from mucosal lesion favors syphilis.	T bercle bacilli often present in sputum and smears from mucosal lesions.
Pseudot bercles (rare) when present are coarse (5 t 10 mm. in diameter)	Elementary and characteristic lesion is the apple-jelly nodule or subcutaneous tubercle, 2 t 5 mm. in diameter

ordinarily invisible in the pink or red of the inflammatory base, but can be detected by expressing the blood from the tissue with a glass spatula, "dia scope," or even the lip of a tumbler or a heavy microscopical slide When thus viewed under glass pressure, the brownish, translucent miliary tubercle, 1 or 2 mm. in diameter stands out clearly against the pale background. The term "apple-jelly" is suggested by its color The apple-jelly nodule is not always present in tuberculous processes in the skin. In certain cases of dry erythema tous tuberculosis, especially of the skin of the face, it may be impossible to identify them. Likewise in certain violently ulcerative tuberculodermas, no signs of tubercle formation can be detected in the gross. On the mucous mem branes the tubercle can be identified as a minute pale granule on the mucosal surface the lesions often being present at a considerable distance from the active ulceration. The hypertrophic nodose tuberculosis of the nose and vegetative tuberculomas (Fig. 569) do not present typical apple-jelly tubercles,

but rather translucent ridges and agminate masses that may be closely imitated by syphilids. The verrucous type of tuberculosis, usually a reaction to



Fig. 474.—Method of demonstrating pple-jelly nodules (tubercles) in cutaneous tuberculosis. This is the sit of primary inoculation with tuberculosis, and practically nothing was visible in the reddish inflammatory scar until glass pressure was pplied (B) with diascope. The ring of miliary tubercles is then easily seen through the glass.



Fig. 475.—The persistence of tubercles in the scar of lesion is one of the important aids in differentiating tuberculous from syphilitic lesions. This is depressed atrophic noncontractile scar studded with miliary tubercles. A lesion, hose border more closely suggests syphilid, is shown in Fig. 456.

direct cutaneous inoculation, may present no tubercles even on histologic examination. Fortunately although its configuration (Figs. 503 504) may

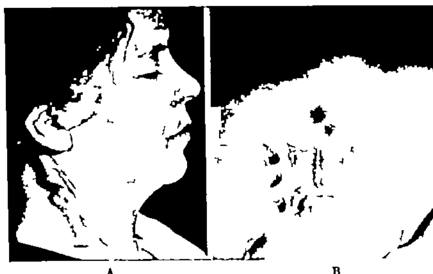


Fig 476.—Indurated scar (A) following removal of gummatous glands. B, Cartwheel spread of gummatous tumor following incision. For history see Fig 477

Fig. 477

A SIX YEAR MASQUERADE OF SYPHILIS AS SURGICAL TUBERCULOSIS

A woman, aged thirty married (see Fig. 476)

Family History: 3 children, one miscarriage. Later questioning disclosed one premature birth, child dying in three weeks.
Complaint: "Boils, Stiff Neck, Scrofula. Pain in the hip six years go, especially nocturnal, worse when at rest.
Treated by Doctor Four Months for Rheumatism. Got worse. Consultation called.
"Boil" on Hip Opened by Doctors. Bone scraped. Told it was tuberculous.
Opened Lesion Refused to Heal. Two more operations, bone removed at each. Worse for time, finally healed.
N Ankylosis or Stiffness of Joint.
Developed "Boil" on Left Shoulder Last Winter Lanced, but did not heal properly Still having trouble.
Boils Appeared on Neck Four Years Ago. Opened by physicians and kept open. Patient told she had scrofula. Painful lumps, stiffness now
Three Operations on Neck.
Coughs Good Deal th Past Six Years especially past nine months. No night-sweats or hemoptysis. Weight loss 9 pounds.
First Examiner Reports "Left shoulder posterior, number of indurated lumps, scars from incision of old boils.
Otolaryngologist Advises Removal of Tonsils and -ray to glands and induration in neck.
Medical Advice, after negative chest ray the same.
Blood Wassermann Report Returns Strongly Positive. Is Repeated, Same Result.

Four Suspicion-arousers Miscarriage, bone sequestrum, refusal to heal, infiltration of scar
"Boil" and carbuncle, together with sarcoma and tuberculosis, are common misinterpretations of the gumma. The oldest child has heredosyphilis.
When Nodule or Tumor in or Beneath the Skin, on Incision, "Cartwheels" Out Into Ring of Nodules About an Infiltrated Scar or Unhealed Wound, Suspect Gumma.

suggest a syphilid the structure of the papillomatous, warty lesion is more that of blastomycosis than syphilis.



Fig. 478.—An infiltrative syphilid of the subcutaneous tissue, suggesting so-called nodal tuberculosis of the fascia, associated with lesion of the larynx and vocal cords, thought t be tuberculous. Serological reactions positive, prompt response t treatment for syphilis. Surgical exploration for biopsy before the serological test was taken.



Fig. 479.—An exceedingly superficial type of tuberculosis on the buttock. Note the resemblance of the superficial trophic scar to that of syphilis. Even the border is distinctly suggestive. Not however the miliary reddish-brow point in the active part of the lesion. These are too small and too numerous for gummatou foci. The lesion is of fourteen years duration and began in childhood. While t time syphilid may have duration of years, th longer cutaneous lesion lasts, th more probable is it that it is tuberculous. This is especially true if the lesion begins *in childhood or early adult lif*

I our experience the most difficult differential problems involving cutaneous tuberculosis and syphilis have occurred in lesions on the face and the buccal mucosa. These are illustrated in connection with the regional topography of late syphilids of the face. In spit of the use of every diagnostic resort, one is occasionally left with an uncertainty as t whether the lesion with which he ha been dealing is tuberculosis or syphilis (see Figs. 460, 502) In some cases biopsy animal inoculation, and prolonged mercurial therapeutic tests are needed t establish the diagnosis.

Differentiation of Late Syphilids and Certain "Tuberculids. —This problem has been touched upon to some extent in discussing the differential problems of secondary syphilids. The tuberculoma which is most likely t be confused with late syphilid, is the indurative tuber culous plaque known as erythema induratum. This lesion usually develops upon the inner posterior surface of the leg above the ankle in young omen ho are inclined to overweight, anemia, and amenorrhea (Fig. 516) The background is that of an occult tuberculosis, and the lesion itself is tuberculous as shown by animal inoculations, though the histologic architecture is rarely typical. Clinically the pink to purplish, brawny infiltrations are quite typical to the experienced. The central portion of the plaque tends to soften and break down, but ulceration is rarely ex tensive at any given time, and the typical configuration of late syphilids is usually lacking. The plaque of erythema induratum is often composed of group of coalescent papulonecrotic lesions

Fig 480.

DIAGNOSTIC POINTS COMMON TO BOTH CUTANEOUS TUBERCULOSIS AND SYPHILIS

1 Apple-jelly nodules may occur in both conditions, but are much rarer in syphilis.
2. Localization upon face and nose occurs in both and furnishes some of the most difficult problems.
3. Thin trophic scars occur in both diseases.
4 Weak or biologic false positive Wassermann reactions may occur in tuberculosis by older technics and highly cholesterinized antigens.
5. A Herxheimer reaction t arsphenamin may occur in both processes.
6. Frambesiform, nodular and hypertrophic lesions may occur in both diseases.
7 Adjacent lymphatic glands may be involved in both diseases.
8. Constitutional symptoms may closely simulate each other:
   Pulmonary symptoms.
   Lymphadenitis.
   Bone involvement.
   Loss of weight, fever night-sweats, gastric disturbances.
9 The Von Pirquet reaction does not differentiate them.
10. Improvement and even symptomatic cure (?) may occur under arsphenamin treat ment, and even improvement under mercury (slight) and iodids.
11. The histologic pictures may sufficiently resemble each other occasionally to confuse the pathologist.

with their central plugs replaced by softened and broken-down mass. The lesions are often markedly tender in contrast to syphilids. The finding of the essential lesion of the tuberculid—the necrotic centered papule shown in Figs. 553 596 and 548—is sometimes essential to diagnosis.

A vigorous warning should be given gainst dependence on arsphenamine for the therapeutic differentiation of the tuberculids. The non-specific effects of this drug have been discussed in Chapter V but need reiteration in this connection. If in the absence of expert consultation therapeutic test must be resorted to, it should always be with mercury alone.

The scars of erythema induratum often furnish the closest imitations of those of syphilids with which we are familiar Their localization (Fig. 557) on the posterior surface of the leg, and their usual lack of characteristic configuration (exception in Fig. 557 A) may be the chief dif ferential points. In peripheral hyperpigmentation and in character of scarring they may be remarkably deceptive. The finding of the scars of tuberculid (folliclis) on the hands (Fig. 548) is occasionally an important aid.

Scrofuloderma, the bluish-red soggy inflammatory skin which surrounds the openings of tuberculous sinuses, is often thought to be distinctive of tuberculosis. It seems not to be generally known that deep syphilitic process may drain through sinus after gummatous softening, especially in the case of bone and joint involvement, and confusion of syphilis and tuberculosis

occasionally results (Figs. 607 611) While a species of syphilitic "scrofuloderma occasionally develops, there is more of tendency of the syphilitic process to take on the configurations of lat syphilid in the process of extending into the skin.

"Tuberculosis colliquativa, recently reviewed by Michelson, may at times reproduce the indurated plaque type of late syphilid with multiple points of ulcerative breakdown. In the nodular stage, Michelson states, differentiation may be almost impossible without serological nd bacteriological findings. Tuberculosis is of a cyanotic blue color syphilis more a rusty red. The tuberculous scar is thick and keloidal, that of the syphilid thin and atrophic. The syphilitic ulcer border is punched out and indurated, the tuberculous border is thin, irregular and undermined. The differentiation of "nodal tuberculosis of the fascia (Figs. 478, 480), tuberculous gumma (Fig 539) and the tuberculoid "sarcoids (Fig. 515) is presented in connection with



A B

Fig. 481 —Typical lesions observed in patient ith maculo-anesthetic lepra. I A note the peering gaze and infiltrated brows the enlarged nipples the pudgy hands. This patient knees are shown in B. The ulcers are due t burns resulting from contact with hot radiator pipe adjacent t the patient bunk in lumber camp. The ulcers had been diagnosed syphilitic, but the blood Wassermann reaction was negative. Traumatized knees of which the patient makes no complaint should arouse a suspicion of lepra. The ulnar nerve was three times normal size, nodular and insensitive The nasal smear teemed with intracellular acid-fast Hansen bacilli. There were of course, extensive nerve changes.

the case histories and figures (see also Chapter V) All these lesions have the disconcerting peculiarity of responding t systematic arsenical therapy so that they furnish fertile field for error in the practice of those ho re unfamiliar with the nonspecific peculiarities of these drugs

Combinations of Syphilis and Tuberculosis in the Skin.—These are less uncommon than one would imagine, and especially in young people may be highly confusing One of us (J.H.S.) has seen combined syphilis and lupus vulgaris of the nose involut partially under mercury the remainder of the cure being accomplished by tuberculin. In view of the curious combination of nonspecific effects secured from the arsphenamine treatment of tuberculosis and tuberculids and the tuberculin nonspecific treatment of syphilis, it must be conceded that many cases will be impossible of differentiation into their component parts. Examples of such problems are presented in Figs. 538 and 539 I those cases which have studied the distribution and characteristics of the

combined process seemed to point to the tuberculosis as primary and the syphilid as superposed. Fusion types combining syphilis and tuberculosis have received increasing attention in the recent literature, including articles by Fernet, LeBaron, and Bloch-Michel (1933), Gougerot, Lons, and Dreyfus (1936), Gougerot and Boulle (1936) (tuberculous pseudochancre) Tomé Bona (1930) (Vignolo-Lutati lymphatic syndrome) Salbene (1930) (lupo-syphilitic hybridism of nose and jaw in heredosyphilis) Sergent and Longjumas (1930) (syphiloscrofula)

The Differentiation of Cutaneous Late Syphilis and Leprosy—Leprosy and syphilis, especially in temperate climates, where the former disease is not indigenous and therefore unfamiliar are so commonly confused that it is unusual to see leper who has not been diagnosed syphilitic and usually treated for the disease There can be no doubt that the differentiation is at times exceedingly difficult and that the occurrence of positive blood Wassermann reaction

Fig 462.

THE DIFFERENTIATION OF CUTANEOUS LATE SYPHILIS AND LEPRA

Late Syphilis.	*Lepra (mixed and nodular)*
Evolution more rapid than that of lepra.	Evolution usually extremely slow
Seldom diffusely infiltrates face, brow and ears.	Distinct tendency to infiltrate face, brows, and ears.
Lat alopecia of eyebrows and scalp rare or unknown.	Alopecia of eyebrows and scalp common.
Tendency to ulcerative breakdown more marked.	Tendency to ulceration of lesions slight (ulcers usually trophic or traumatic)
Ulcers have typical configuration.	Ulcers lack configuration.
Coincident laryngeal changes possible, but unusual.	Coincident laryngeal changes common.
No nodular enlargement of ulnar nerve.	Ulnar nerve enlargement and insensitiveness quite distinctive.
Atrophy of interossei rare, but possible (motor neuron disease).	Atrophy of interossei common.
N claw-hand (main en griff)	Contracture (main en griffe) common.
No blue, pudgy "Morvan" hands.	Morvan or syringomyelic or peripheral neuritic hands.
N depigmentation associated with nerve changes.	Depigmented areas associated with nerve changes.
Dissociation of pain and temperature or complete anesthesia rare. Hence no burns.	Complete regional anesthesia and loss of pain-temperature sense common, hence severe burns (knees, hands, etc)
N characteristic association of nerve changes and skin lesions.	Annular infiltrates with central depigmentation and anesthesia common.
Changes in the nervous system of central origin chiefly	Nerve changes preponderantly those of peripheral neuritis.
N sal smear negative for Hansen bacilli.	Nasal smear may show Hansen bacilli (or may not)
Smear from papule or nodule negative for bacilli.	Smear from papule may (or may not) show bacilli.
No hypertrophy of male nipple.	Hypertrophy of male nipple not uncommon.

in some 80 per cent of lepers by the older technics has not helped to clarify the picture. As with tuberculosis, the differentiation of each case is an individual problem, fitted with difficulty into any summary scheme. It is possible to find exceptions to almost any dogmatic differentiation. None the less the following points are of material assistance in distinguishing the commoner chronic mixed and nodular types from late syphilis.

The differential problems are most difficult in the earlier stages of the disease, when, as in Figs. 349, 481 the hoarseness, alopecia of the eyebrows, papules and nodules in the face, macular eruption on the trunk, and perhaps circinate or gyrate infiltrate or two, are remarkably suggestive of syphilis. The arousing of suspicion begins with the facies and the bluish hands (Fig 462), for one rarely sees pure anesthetic type without skin lesions. Burned or traumatized knees (Fig. 481) structures of which the average person is extremely careful, should always arouse suspicion of lepra. In one of Stokes patients the first clue (anesthesia) was his story that he had

been vexed by toe that would not heal, and placing the foot on box, had shot the offending member off ith revolver It is alw ys well t go over the extremities of patients with infiltrated



Fig 483.—The bluish pudgy hands of the leper whose back is shown in Fig 484. Not the glossy "trophic" skin of peripheral neuritis.



Fig. 484 —Typical lesion of maculo-anesthetic lepra. Thi patient in nine years had been seen by seven physicians, most of whom had evidentl made diagnosis of syphilis, t judge from the treatment he had received. The large nnular lesion on the inner spect of the left forearm is a typical annula infiltration ith central anesthesia nd depigment tion The diagnosis confirmed bacteriologically

facies, using pin t detect areas of complet anesthesia, no matter hat the appearance of the eruption or the blood serologic findings may be A smear should then be made from the nasal mucosa or from nodule and stained (Ziehl Neelsen) for acid-fast intracellular organisms The

finding of an enlarged nodular and insensitive ulnar nerve is of the greatest assistance. The unusual possibilities of confusion of cutaneous lepra with syphilis are well illustrated by a case seen before a dermatologic society in which able observers believed the infiltration of the face and ears to be syphilis, and the squamous leprous eruption on arms and legs to be an arsenical dermatitis following arsphenamine treatment. Late lepra, with leonine facies and neurotrophic changes, is usually only a problem to the inexperienced. It must be recalled that syphilis and leprosy cannot be differentiated from each other by blood serologic tests for syphilis which are biologically falsely positive for syphilis in so high a proportion of cases of leprosy that they are best wholly distrusted until such time as biologic false positives can be distinguished from true syphilitic positives. The existing verification tests to date do not provide such a differentiation. The diagnosis of leprosy must therefore be positively made by the finding of the organism or other means. For those who require the latest information on the immunobiologic diagnosis of leprosy reference should be had to the article by Pardo-Castello and Tiant (1943).

The Differentiation of Syphilis and Sporotrichosis.—The response of sporotrichosis to iodides, and the existence of a deep gummatous type is responsible probably for a not infrequent confusion of this disease with syphilis. The various types of sporotrichosis and their differential diagnostic characteristics have been recently admirably reviewed by H. Foerster. The sporotrichotic gumma, probably representing a hematogenous infection, is rare in this country and

Fig 424.

DIFFERENTIATION OF CUTANEOUS LATE SYPHILIS AND SPOROTRICHOSIS

Syphilis.	*Sporotrichosis.*
Inoculation focus not present.	Site of inoculation often recognizable, but not invariably.
Nodules tend to be in the skin at the outset.	Nodules under the skin (lymphatic) at the outset.
Arciform and polycyclic configuration the rule.	Linear distribution the rule.
No chain formation of satellites along the lymphatics.	Marked tendency to chain formation along the lymphatics.
Little tendency to adjacent lymph-node involvement, comparatively.	Marked tendency to lymph-node involvement.
Culture negative for sporothrix.	Culture usually positive for sporothrix.
Collateral evidence of syphilis.	Wassermann shows no tendency to false positives.

usually will require cultural differentiation. The lymphangitic types seen in this country and shown in Figs. 504–505 have the following differential points.

The very great importance of culture (4 per cent maltose agar at room temperature) should be stressed for doubtful cases. There is nothing characteristic in the histologic picture of sporotrichosis upon which diagnostic reliance may be placed. The lesions of sporotrichosis seem to show a tendency to earlier breakdown than those even of a gummatous syphilid, and aspiration of the earliest nodules will often yield pus with a pure culture of the organism. Therapeutic tests are very unreliable indeed. In a case clinically diagnosed a syphilid on our service and treated exclusively with arsphenamine and mercury (no iodide or roentgen-ray) after healing had taken place, the laboratory presented us with a beautiful culture of sporothrix, fortunately obtained from the lesion in the routine procedure of differentiation before treatment was begun.

Differentiation of Late Syphilis and Blastomycosis.—The lesions of blastomycosis are the least likely of the granulomas to be confused with late syphilids, yet confusion can and does occur (Figs. 504, 567). The lesion produced by the blastomycete is clinically a papilloma, containing numerous epidermal abscesses, from which exude on pressure minute droplets of pus containing the organisms. The cutis is involved in the inflammatory process, and with the peripheral extension of the infection a thin but often tough and deforming scar may develop. The configuration of the lesions is perhaps the most suggestive feature of a syphilid, yet the arciform tendency is not marked and lacks the frequently exquisite definition and striking character of the late syphilitic contours. The pathologic picture of blastomycosis, the epithelial abscesses containing the organism in tissue sections from untreated cases, the papilloma, and the finding

Phagedena Geometrica (Broca); Pyoderma Gangrenosum; Microaerophilic Streptococcal Infection and so forth.—This title includes large group of ulcerations of chronic type with undermined policyclic borders and tendency to persist, recur and grow in spurts, in spite of vigorous attempts at local therapy. They may be primary or secondary to such conditions as local trauma (post-operative), chancroid, chancre, pyoderma, syphilid, colitis, or empyema. The borders of the ulcers are typically boggy bluish, soft, undermined, serpiginous and ragged. The base is moist and covered with mucopurulent exudat The tissue has a "melted out" appearance with little or no tendency to granulation. When healed, the scars are parchment-like, slightly pigmented and indistinguishable from those of syphilids. I the type described by Meleney especially (1924 1930) various types of organisms, particularly hemolytic and nonhemolytic streptococci, the hemolytic types growing t low oxygen tension ("microaerophilic"), with



A B

Fig 487—Differentiation of psoriasis, seborrheic dermatitis, and lat syphilis of the scalp nd forehead

The trophy which distinguished A and B is easily seen in the fine wrinkling of the skin of the entire forehead hen the brow are contracted. Definite scarring is visible. Not that while the process involves the inner canthus of the eye there is no sign of cicatricial contraction. The process in the psoriatic is much more superficial and ther is no sign of permanent damage to the skin.

The syphilid in the patient here show as considerably more extensive than ppears in the photograph. There was large patch over the left shoulder another over the sacrum. Serious bone involvement had occurred, with necrosis of the skull show in the photograph and destructive arthritis of the elbows nd knees. It is worth remembering that arthritis may accompany psoriasis and momentarily confuse the picture with syphilis. This patient blood Wassermann reaction was positive her spinal fluid negative. She had lost 40 pounds in weight. The recovery under treatment as phenomenal.

The necrosis of the skull in A would clinch the case for syphilis if all other signs failed. Yet in Fig. 501 is shown the case of woman ith very similar lesion of the skin of the forehead and face and necrosis of the frontal bone who was treated for five years by various physicians for eczema thout having her syphilis recognized.

hemolytic staphylococci and other types of organisms occur in symbiosis. The lesions may appear on any part of the cutaneous surface, ncluding the center of the face most frequently on the extremities and genitalia and occurring in the axilla complication of hydradenitis suppurativa. They are differentiated from syphilitic ulcers by their acut ppearance, rapidity of development, bogginess in place of induration, undermined borders, and lack of spontaneous tendency t heal (Brunsting, Goeckerman and O'Leary 1930, Greenbaum, 1911)

Epithelioma of the Skin.—This important diagnostic problem differs from some heretofore considered in that it is occasionally wiser to err in the direction of a too ready diagnosis of epithelioma than of a neglect of epithelioma in favor of syphilis The essence of differentiation in the majority of cases lies in a study of the border of the lesion (Figs. 40 507 316 615 see also Chapter

XI) The elementary lesion of epithelioma of whatever type is the pearly nodule with faint superficial telangiectases over the surface. Occasionally the border of an epithelioma may fail to show distinct "pearling," and suspicion as to its character be aroused only by the hardness and resistance of the tissue. A rolled border on any lesion, regardless of configuration or other features, at once draws epithelioma into the differential diagnosis. While squamous-cell epithelioma the more malignant type rarely shows any tendency to a healing reaction, basal-cell epithelioma may show marked evidence of healing and in the mildest types give rise to a smooth, depressed noncontractile scar with an active margin not a little suggestive of a syphilid. Squamous-cell epithelioma gives rise to ragged excavations which are not suggestive of syphilis basal-cell epithelioma, on the other hand may produce a superficial ulceration quite suggestive of an ulcerative late syphilid. In the so-called "Paget-like" forms of epithelioma originating often in the hair follicles and sweat glands ("tubular" type) the process may wander about the skin of the face and neck for a period of years, producing scarring quite suggestive of a syphilid, or extensive partially denuded areas whose outline may seem suggestive, and whose slightly raised border may have a distinct induration albeit likewise usually a suggestion of a pearly sheen. Epithelioma of the skin does not in general rise from cutaneous gumma, differing in this respect quite sharply from the notorious tendency of gumma of the mucous membrane to become epitheliomatous. In large doubtful lesions an examination of tissue from the margin may be made. Small doubtful lesions may be excised entire, and biopsies should be taken from suspected lesions about the lip or on the buccal mucosa, though there is difference of opinion as to the risk of producing metastasis in this way It is certain that manual and instrumental manipulation of doubtful lesions is undesirable from this standpoint, so that squeezing and pinching lesions as a test for induration and hardness should be reduced to a minimum. (Class demonstrations especially) The presence of preepitheliomatous lesions such as the senile keratosis always swings the diagnosis of an ulcerative lesion in favor of epithelioma.

In the differentiation of epithelioma from syphilids of the mucous membranes the presence of preepitheliomatous lesions and of sources of irritation is likewise important. Leukoplakia of the mucous membranes and lip (Figs. 417-481) at once throws the burden of proof upon the contender for syphilis, for the high malignancy of mucosal epithelioma makes an erroneous diagnosis of syphilis, to the exclusion of epithelioma, almost inexcusable It is, in general, safer t regard suspicious lesion on the mucous membrane, and especially the tongue as an epithelioma until it is proved otherwise. Malignant lesions in these situations show tendency to cauliflower growth, rolled margin and hardness to touch which can usually be readily recognized. All ulcerative lesions on the mucosa should be checked by the blood serologic test, and if positive, one or tw arsphenamine injections may be given in two or three days as therapeutic test. *This must not, however be regarded as sufficient*, and examination of tissue from suspicious parts of the lesion should be made at the same time (cautery excision if possible) to rule out the possibility of malignant degeneration in gumma. Arsenicals have no significant effect on uncomplicated epithelioma, so that no nonspecific effects need be guarded against, and mercury because of its slowness should not be used. Pain or lack of it is an untrustworthy criterion in distinguishing malignancy from syphilis of the mouth and throat, for an epithelioma may progress to hopeless state before many patients begin to make complaint.

The patient bo has developed epithelioma as complication of gumma in the mouth or throat should be vigorously treated for syphilis after operation and radiotherapy have been begun. Stokes has seen patient ith syphilis who had sustained hemiglossectomy for car cinoma of the tongue develop second carcinoma upon gumma ppearing in the remaining half of the tongue. The positive blood serologic reaction, identified before his previous operation, had been ignored.

Endothelioma Capitis, Angiosarcoma (Endothelioma) and Fibrosarcoma.—The endothelioma of the scalp (Kaposi) is multiple nodular tumor of the scalp which may occasionally be *momentarily mistaken for gumma by those unacquainted with the existence of the neoplasm.* The condition is essentially multiple basal-cell epithelioma. Angiosarcoma or endothelioma of the skin (Fig 571) may be confused with syphilis and may show temporary response to arsphenamine therapy The necrosis of bone and the often circinate margins of the ulcerative lesions add color to the deception. The elementary lesion of the angiosarcoma is nodule in the skin which rapidly undergoes necrosis, forming a punched-out ulcer not unlike a small broken-down gumma. The pathologic diagnosis must usually be made from these earliest lesions, for the margin of the larger ulcers assumes a granulomatous structure from secondary infection. Two of the three cases under our observation had been diagnosed and treated as syphilitic for considerable periods, and one



A B

FIG. 456.—WHEN LATE SYPHILID SIMULATING PSORIASIS APPEARS UPON THE ELBOW WHAT DIFFERENTIAL CRITERIA SHALL W INVOKE?

These two photographs tell the story of the gross morphologic differentiation in the majority of cases.

Psoriasis (A)

- Note that though the lesion is annular there is no induration. It is flat and superficial.
- Note the abundant dense imbricated silvery scale which is characteristic of psoriasis. The black spots are the intense red surface of the underlying papular lesion.
- Note that there is no atrophy and there are no scars.
- A typical capillary hemorrhage occurred from the abraded areas.

Late Syphilid (B)

- Note the fleshy look, the appearance of induration.
- Note the arciform grouping of the major lesions. Not the scantier scale and its thinner more friable quality
- Note the trophy where lesions have involuted. Note the scars.
- N capillary hemorrhage could be obtained from the abraded lesion.

of them had almost healed under such management. The fibrosarcoma occasionally produces lesion which suggests momentarily nodular syphilid The so-called "Kaposi hemorrhagic sarcoma of the leg relatively rare tumor seen oftenest in person of Jewish race, is nodular infiltrative and plaquelike lesion of the lower leg, associated with quite distinctive hemorrhagic changes in the skin, leading t characteristic pigmentation and color changes.

The Lymphomata of th Skin and Mycosis Fungoides.—Leukemic and Hodgkin infiltrations of the skin may occasionally produce lesions quite resembling late syphilids in color feel, and configuration (Figs. 531 532) They are rarely ulcerative Under roentgen-ray treatment, nd at times spontaneously they may involut leaving slight trophic remains or no traces whatever The lymphatic leukemias give rise occasionally t extensive papular eruptions that may suggest



Fig. 489.—This presents a circinate type of seborrheic dermatitis which has been described as seborrhea petaloides. Less marked examples of the same variety of this dermatosis have been described by Toyama. Note that the location of the lesion is at one of the sites of predilection for seborrheic dermatitis (scalp, face, presternal, and interscapular region). The lesions form on a seborrheic base, the skin being oily and the follicles patulous and plugged with sebaceous material. The circinate lesion is pinkish-yellow in color; there is no induration, and the scale is greasy and yellowish. On curetting it off no papule or induration remains. There are no signs of scarring or atrophy. (From the collection of the late Frederick G. Harris.)



Fig. 490.—A form of lichen planus which, when identified, may assist in differentiation of lesions which imitate syphilids. This is the hypertrophic type with dense adherent keratotic scale and may be confused with the keratodermic syphilid. Typical lesions of lichen planus may be identified, usually about the knees, wrist, genitalia, or mucous membranes. This woman had every known lesion of lichen planus at one and the same time except the bullous type. She had twice been told she had syphilis.

syphilids. They involve the face, trunk, and extremities; the papular lesions are firm and indurated; they do not scale, and they are usually intensely pruritic (often suggesting prurigo). The

blood picture usually identifies the process. The loss of hair from involvement of the follicles, affecting the eyebrows especially is often seen in the massive nodular infiltration of the face, which is especially common in splenomyelogenous leukemias. They often suggest late syphilids and lepromas. The removal or grinding down of hair in such region as the eyebrow as a result of rubbing and scratching, must not be confused with true alopecia.

Mycosis fungoides, lymphogranuloma of unknown cause presents two distinct types—the chronic and the "type d'emblée. In the former a prodromal period of months or years may be marked by furiously pruritic dermatitis, often involving the entire body or confined to patches. The surface involved in the dermatitis presently becomes infiltrated, and brawny plaques and circinate gyrat nd annular indurations appea (Fig 485). This tendency to lymphogranu-



F g 491 —This patient, grocer forty-three years of age came t the clinic complaining of an eruption on his forehead. On examination group of lesions, similar t those shown in the photograph but with the arciform character more pronounced and some ulceration in addition, of whose existence the patient was unaware as found over the left scapula. H had, however had patch that he knew of on the buttock very similar in character to the forehead lesion Eighteen years before the patient had had penile lesion with bubo, but no secondary eruption. There was no record of any treatment.

Th blood Wassermann reaction was negative. None the less diagnosis of syphilis was made and treatment begun.

The spinal fluid showed WR negativ 0.3 cc., Nonne positive 92 lymphocytes.

The bone conduction was reduced, right, —7 seconds; left, —9 seconds.

Th fundus of th eye showed mild neuroretinitis.

The lesion involuted rapidly following th institution of treatment.

Not that in spite of the bnormal spinal fluid the neurologic examination as negative (except for slight nystagmus) The patient was an uncontrollable morphine addict and left before treatment was completed.

If patient presents susp.cious but rather anomalous lesion, as in this case, careful search of the entire skin surface and the mucous membranes may as here disclose lesion more typical in ppearance but of hose existence the patient is una are.

The collateral findings here given illustrat defects in th complete work-up of th case. The spinal fluid Wassermann as done on only 0.3 and 0.4 cc though it might have been positive on 1 cc. A provocative test might have been done but as overlooked. The record is inadequate in that no history of previous treatment or statement that none had been given as included

Never accept patient's statement that ther is nothing to be seen. Se for yourself.

lomatous change becomes more marked, nd t mors develop, often undergoing rapid breakdown and ulceration, nd again growing t enormou size before degeneration occurs. Many of these ulcerative lesion have the configuration of syphilids. I the "type d'emblée there is no prodromal or premycotic dermatitic stage the first lesion to ppear being tumor which rapidly breaks down, often strikingly resembling an ulcerating gumma on the leg. The histology of these lesions is quit characteristically that of lymphogranuloma, and the course of authentic cases of both types is practically invariably fatal. Striking responses to combination of arsphenamine and roentgen-ray have been reported. Itching nd history of dermatitis, or evidence of its presence, with the characteristic histopathologic picture in the infiltration may mak the diagnosis early The condition is, fortunately rather rare

NODULAR AND HYPERTROPHIC SYPHILIDS OF THE NOSE

Late syphilids of the nose may bear a striking resemblance to hypertrophic tuberculous lesions of this part of the face, and to acne rosacea and rhinophyma. The underlying inflammatory background tends to conceal the char-



Fig. 482.—Typical superficial syphilids of the nose. A is the nodular syphilid often erroneously diagnosed acne rosacea or lupus vulgaris. Note the coarseness of the nodules and the individual nodular ulceration. Case B is almost duplicate of A, yet B is lupus vulgaris (tuberculosis) and A is syphilid. The typical miliary apple-jelly nodule could be identified in the skin in Case B. C represents the lesion in Case A (syphilid) after treatment with mercury and arsphenamine. Note the completeness of the involution, the small amount of residual damage, and the cat-scratch scarring. D represents syphilid beginning at the bridge of the nose and wandering downward toward cheek and lip. Note the configuration and border and the entire lack of deformity from scarring, hich greatly simplify the diagnosis.

cateristics of the process. The principles outlined in Figs. 410 473 474, 496 may differentiate a late syphilid from lupus vulgaris, but there is no form of *the diseases involved in which the therapeutic test with mercury or a biopsy* must be resorted to more often for a decision. Arsenicals are not to be trusted for these therapeutic tests and mercury may even yield momentarily perplex

ing results (Fig 499) The status of bismuth in such tests is still uncertain. If biopsy is done, a shaving from the skin over the ala if it is involved will usually leave almost no scar provided the cartilage is not nicked

The scarring produced by a syphilid of the nodular type in this region is quite characteristic (Fig 492 C) The individual nodules heal, leaving "cat scratch marks, the process between them simply fading out with some transient pigmentation. The tuberculous process leaves a more pronounced diffuse atrophy and scarring and is rarely so superficial as the syphilid. It is much more likely to leave the nose pinched and shrunken, with loss of tissue in the alae, producing a "bitten out" appearance (Fig. 494 C) This may however occur in syphilis (Fig 498) The residua of a severe acnitis (tuberculid) should be noted in Fig 362, as a possible source of confusion.



Fig 493.—A nodular syphilid of the upper lip and nose The active parts of the lesion were of livid color but at no time had there been any ulceration. The scarring is none the less apparent over the ala. We have seen this lesion almost duplicated by verruca vulgaris of the upper lip.

Rhinophyma and acne rosacea develop on a seborrheic base, with vascular dilatation over the so-called "rosacea oval," including the nose the adjacent infra-orbital region, the skin between the eyebrows, and over the chin. The seborrheic base with oiliness, follicular dilatation and above all comedone formation, is an essential part of the process. The elephantiasic hypertrophy of the "rum blossom" (rhinophyma—Fig 495) does not present the elementary nodular and ulcerative lesions or the crusting of the late syphilid though there may be pustules. In some rosaceas there is simply a nodular hypertrophy without definite comedone or sebaceous cyst formation. When a syphilid develops upon a rosacea the differential diagnosis may become still more difficult, and must depend largely upon the finding of characteristic scars and atrophy at some point where the process has undergone involution The extension of a syphilid downward on to the face (Fig 492, D) assists greatly in diagnosis. If the blood serologic reactions are negative other signs of the disease may be developed by a full investigation.



Fig. 404.—A is the tuberculous lesion known as "lupus vulgaris erythematoides, dry non-ulcerative form of tuberculosis whose configurations may suggest those of syphilid. Both border and scar are studded with apple-jelly tubercles. Note the absence of cicatricial contraction in which this case suggests syphilid. (Collection of F G Harris) B is typical ulcerative lupus vulgaris ith the resultant ectropion. *The bridge of the nose presents* scar containing numerous t bercles. The nasopharynx is involved. Note the pinching and shrinkage of the tip of the nose more suggestive of tuberculosis than syphilis. C is the condition kno as tuberculosis orificialis faciei, form of tuberculosis developing by extension from mucous membranes. The larynx, pharynx, nasopharynx, and lips are all involved, condition decidedly against the diagnosis of syphilis, hich rarely involves skin and adjacent mucous membrane unless occasionally at the commissures. The deep involvement of the cartilage and the destruction of the ala, less common in syphilids which involve the skin of this part of the face, was apparent in C.



Fig 495.—Rhinophyma, condition t be differentiated from hypertrophic syphilids of the nose. (Collection of Dr John A. Fordyce.)

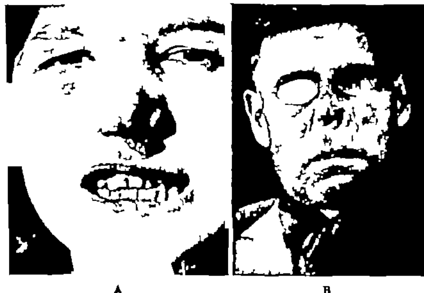
DIFFERENTIAL DIAGNOSIS OF DESTRUCTIVE LATE SYPHILIDS OF THE NOSE

The destructive types shown in Figs 497 and 498 differ decidedly from the nodular and tuberous late syphilids of the skin of the nasal region. In these lesions again the confusion of tuberculosis, syphilis, epithelioma, and of rhinophyma and rhinoscleroma at the outset is easily possible. Some important differential clues are summarized in Fig 496

The differentiation of syphilis from rhinoscleroma depends upon the intrinsic rarity of the latter in this country the *hardness* and keloidal sheen of the hypertrophic tissue (usually the ala nasi) the late occurrence, or more usually absence of ulceration the hypertrophic cicatricial changes in the pharynx, and the finding of the bacillus of rhinoscleroma in excised tissue

DIFFERENTIAL DIAGNOSIS OF DESTRUCTIVE LATE SYPHILIDS OF THE NOSE

1 A destructive lesion beginning on the septum is more apt t be syphilid than tuberculosis or epithelioma. *Syphilids perforat septum and palat in preference to other cartilages of the nose*
2. The more radically and rapidly destructive of the deeper tissues, the more the diagnosis tends toward epithelioma.
3. A destructive lesion of the nose which is slow t respond t treatment for syphilis should have an early pathologic examination of tissue taken from the extranasal nd intranasal borders to detect the presence of epithelioma. Some of the reported malignant lat syphilis of the nose is, in reality epithelioma. Bacteriologic study (microaerophilic strep., lepra bacilli, et) desirable.
4 Other conditions requiring differentiation include (a) *septal lesions* including *traumatic perforation* (low down, clean edge), *chrome ulcer* (similar location in chrome workers, other chrome lesions of the skin present), *lepra* (ulcer higher up, intracellular Hansen bacilli in smear); (b) *gangosa* (ya)—extensive destruction of soft tissue and bone strikingly resembling late syphilis; (c) Meleney *microaerophilic hemolytic streptococcal ulcer*—burrowing, undermining, acute, with boggy ragged and bluish borders and a tendency to sinus formation; (d) *diabetic gangrene* of center face—presence of diabetes, exclusion of syphilis; ( ) *rhinoscleroma*—hard hypertrophic lesions bulging into nose and nasopharynx; organisms found in smear and characteristic histology (f) *Hodgkin disease* and other types of lymphoblastoma and leukemia—edema, inflammation, swelling, necrosis, identified by biopsy and blood studies (rare); and (g) *sarcoma*—identified by biopsy
5. Never forget the possibility of factitial lesion produced by escharotics in examining suspected destructive syphilids about the nose (Figs. 497 B and 499)
6. Nasal syphilis involving the bones may be very slow to respond to treatment, which increases the difficulty of diagnosis.
7 The diagnosis of late destructive syphilids of the nose may t times depend entirely upon collateral evidence, no single objective feature or group of signs in the lesion itself sufficing for diagnosis.



A B

Fig. 497.—That the rule of presumptive tuberculosis or epithelioma in the presence of marked destruction of cartilage is not invariable is illustrated by this series of photographs. A is gumma of the septum, causing collapse of the nasal bridge, with extension of the gummatous infiltration on to the upper lip. An exactly similar picture produced in one of our patients, proved after months of treatment for syphilis (Fig. 615) t be epithelioma, originating intranasally nd recognized only when it was too late by biopsy of the edge appearing t the lip. B is a destructive syphilid of the nose with gumma of the septum, treated for some months with radium as tuberculosis ithout Wassermann test. When this was finally taken it proved t be strongly positive and the patient made slow but finally good response to arsphenamine and a prolonged course of inunctions. *Epithelioma must be watched for in such lesions.*



Fig 498 —The active lesion in this case was of exactly the same type as that on the nose of Fig 494, C, yet the former is lupus vulgaris, while the latter was syphilid. The syphilid was identified in the following w y:

1 A scar on the penis with history of lesion in 1900.
2. Secondaries in the scalp. Recurrent mucous lesions at the time
3. Rapid progress of the present lesion. Three months had removed most of the tip of the ala.
4 N detectable tubercles (pple-jelly nodules)
5 N signs of tuberculosis of lungs, throat, larynx, or nose
6. Beginning involvement of the septum. Syphilis select the septum.
7 Leukoplakia.
8. A positive Wassermann series. Th first Wassermann reaction was negative. The series showed *HI HI* neg., *IH IH*
9 An immediate response t treatment for syphilis.

The lesion was then hypertrophic syphilid of the nose These lesions have no characteristic configuration in many cases hich will distinguish them. They must be identified entirely by collateral evidence by elimination of the possibilities of tuberculosis, rhinophyma, rhinoscleroma, microaerophilic streptococcus infection and other forms of gangrene ith ulceration and epithelioma, nd by the effect of therapeutic test for syphilis.



Fig 499 —Note the improvement produced in B as compared with A as result of mercurial therapeutic test. The change took place ith ten daily injections of mercury succinimide—yet the lesion is tuberculous of the skin, w th factitial destruction of the nose by the use of an escharotic past The correct diagnosis was established, after an erroneous diagnosis of syphilis has been made by the failure of the patient t improve beyond the point shown, and the results of biopsy which showed typical tubercles in the periphery of the lesion. Non-specific effects in treatment for syphilis extend even to the use of mercury t some slight degree although experience soon convinces one that mercury is the most trust orthy drug in differentiating syphilis from tuberculosis by therapeutic test.



A B

Fig. 300.

These Two Faces Present a Type of Syphilitic Lesion Often Associated with Involvement of the Bones, which is evidently quite unfamiliar to the medical profession at large to judge by the history of diagnostic errors which such patients usually present.

Case A.—With lesions of the clavicle and sternum as well as of the skin of the neck and face, twenty-three years elapsed from the first appearance of the lesion in this case to the making of the correct diagnosis. The original medical diagnosis was cancer which was subsequently changed by various physicians to scrofula and tuberculosis of the skin. Cautery and local applications of arsenic pastes had been used. **Her First Wassermann Test Was Taken When She Entered the Clinic, June 25, 1918,** at least ten years after the test had become part of medical practice.

The picture is, of course, grossly distorted by local interference with the lesions, but **the Distinction from Tuberculosis** can be based in part at least upon the sharp margination of the lesions with complete absence of the extension of the periphery in the form of apple-jelly tubercles, which is the rule in tuberculous processes. The scars are perfectly clean, and considering the extent and depth of the process the amount of contracture is very slight.

The Distinction from Epithelioma is More Difficult to Make. Although the border is not distinctly pearled, and there are entirely too many lesions for the average epithelioma, it is sometimes necessary to remove tissue for pathologic examination before a diagnosis of benign lesion can be made. This had apparently never been done in this case although destructive treatment had been freely employed. At the present time it would be quite inexcusable to proceed to destructive measures until the identity of the lesion had been established.

A Duration of Twenty-six Years is Not too Long for a Syphilid. It is, of course, also possible in tuberculosis, but hardly in keeping with epithelioma.

Case B.—The first physician to examine this patient in the clinic left the statement in the record, "No skin lesion of lues." The configuration of the lesion and scar below the right malar region is, however, distinctly suggestive of syphilis.

The trouble began with a nodule behind the right ramus of the jaw two years before. An attempt at surgical excision resulted in an extension of the process. There was evidently associated involvement of the articulation, which swelled and the jaw became locked, but later released. No Wassermann test had been taken nor had the patient been treated for syphilis. There was apparently no history of infection. The Wassermann reaction taken after entering the clinic was positive. The response to treatment was prompt.



Fig. 401.

Note the depression in the right frontal region (scarred) indicating loss of bone. The skin lesion is destructive and leaves a superficial thin atrophic scar. Several large but no miliary nodules are detectable in the margin of the active patches. Note, too, that the scar is non-contractile—that the lips meet normally and without distortion.

Twelve years ago at the age of twenty-four this patient was hit on the forehead by a closet door. A small nodule developed, which was excised a year later and with it a piece of dead bone was removed. The lesion would not heal, and two years later more bone was removed and a pedicle graft from the forearm attempted, but without result. The lesion then persisted five more years and healed spontaneously. Then the face became involved, a small nodule appearing near the eye and a moist ulcerative process gradually extending about the face. For five years she had been treated for eczema by various doctors.

From her childhood and adolescent history the following facts stand out. She had had a general eruption at the age of thirteen of an extensive ulcerative type. As an infant she had been ailing and had been constantly under medical care. Following the appearance of the general eruption one elbow had stiffened and partially ankylosed. At the time the lesion on the forehead appeared the tibias had also become tender to touch and had begun to enlarge.

What are the outstanding facts thus far in this case?

1. An extensive ulcerative eruption associated with a bone lesion (stiffened elbow) at thirteen years, before the usual age of sexual experience.
2. A nodule appearing after trauma, which means a local lowering of resistance.
3. Dead bone.
4. A graft that failed.
5. An ulcer that would not heal and more dead bone.
6. Coincident involvement of the tibias.
7. An "eczema" that destroys tissue and leaves a scar.
8. A superficial atrophic non-contractile scarring of the entire face.
9. No apple-jelly nodules in the scar.

Trauma, Nodule or Tumor Incision, Dead Bone Failure to Heal, More Surgery, More Dead Bone, Slow Course, and Final Healing is a Typical Sequence in Clinical Syphilis. The Wassermann reaction was not in general use when this sequence began, but it might well have been invoked later.

Why Not "Eczema"? Eczema is a dermatitis—an inflammatory non-destructive process, producing thickening, not thinning of the skin, and almost never leaving scars. This was, on sight, a Granuloma. The clean non-contractile scar and absence of miliary tubercles (apple-jelly nodules) makes lupus vulgaris improbable and this is the only other granuloma which the picture suggests.

An Examination of the Elbow and the Tibias Should Have Aroused Suspicion.

When after twelve years this patient was finally examined completely it was found that she had a strongly positive Wassermann reaction, a dacryocystitis, and the x-ray picture of syphilitic periostitis involving tibias and left elbow. Neither of these findings was really essential, and the diagnosis could have been made with confidence on the gross examination and history.



Fig. 402.—A coarsely nodular dry lesion of the face strongly suggestive of late syphilid, and subjected to the therapeutic test, with negative results. The condition is an erythemato-squamous and nodular tuberculosis, the nodules being agglomerated masses of tubercles. The response to ultraviolet light was excellent.



Fig. 403.—The configuration, peripheral extension, and central atrophic scarring suggest syphilid. The lesion has, however verrucous, papillomatous scaling border, the scale being densely adherent (not crust). This is tuberculosis verrucosa cutis, beginning at the healed mouths of sinuses from broken down tuberculous lymph nodes. Late superficial syphilids may in the same way occasionally begin at the site of a broken-down gumma, especially following incision or other trauma.



Fig 504



Fig. 505

Fig. 504.—A typical example of blastomycosis on the face The circinate contour papillomatous border and central atrophic scar are apparent. The papillomatous margin is the most important differential point. Tuberculosis verrucosa cutis, blastomycosis, certain basal-cell epitheliomas, and bromoderma are four conditions likely to be confused ith each other but less likely t be mistaken for syphilids if the papilloma be kept in mind (see Fig. 505) Excision of biopsy tissue from suspected blastomycosis, trauma, and surgical curettage of the lesion of blastomycosis may cause generalization of the infection, so that care must be used in diagnostic manipulation. Iodides and arsphenamine may give false therapeutic test for syphilis in these lesions if used.

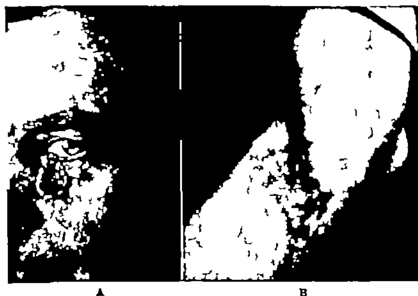
Fig. 505 —Blastomycosis of the pubic region. In its early stages this condition could have been readily confused with inguinal granuloma or syphilis were it not for the papillomatous border (Collection of Dr F G Harris.)



Fig. 506.—Sporotrichosis of the forehead The site of inoculation is above the inner canthus. The preauricular node is enlarged, and pus can be obtained on aspiration, yielding pure culture of the organism. Sporotrichosis is diagnostic problem mainly in the Middle West, and in these regions it is saf rule t take cultures from doubtful lesions on maltose agar especially if there are adjacent softened lymph nodes. The cultures grow at room temperature Iodide cannot be used in therapeutic tests because of its effect on sporotrichosis.



Fig. 507.—The rolled pearly border of epithelioma in man of thirty years. The youth of the patient or coincident syphilis does not infallibly exclude epithelioma from the diagnosis.



A B

Fig. 508.—Gumma of the eyelid resembling epithelioma. The lesion resisted two radium treatments, and later healed under arsphenamine following the finding of a positive Wassermann. At the time, however, the patient presented the late syphilid at the knee which was overlooked. Biopsy reported "granuloma."



Fig. 509.—A factitial lesion on the trunk suggesting syphilid. It consisted of multiple eschars, closely grouped about the umbilicus. The fact that the lesion is in bizarre position, shows no central involution, and presents multiple dry gangrenous eschars at once arouses the suspicion that it is *self-inflicted affair.* The facies of the young girl was typical of the malingering mentality. She cauterized herself with lye to avoid work and arouse sympathy.



Fig. 510.—Indolence, Induration, Arc.

Without warning or apparent reason this man (aged forty-five) suddenly developed swelling on the chin, which broke down and discharged. At first the lesion, which was brawny and indurated, was regarded as carbuncle. It was incised, but did not clear up. Instead others began to appear only to be incised or opened in their turn. After matter of three months or so, in which diagnosis of sycosis satisfied the patient and physician, dermatologist was called.

Unfortunately the photograph cannot exhibit in its full perfection the indolence combined with an almost brawny induration which characterized the whole process. It does, however, show the arc extending under the chin. The beard was intact—not pustule to be found at the time of examination even in the indurated area, which seemed entirely free from the canalization with pus sinuses that characterizes trichophytic sycosis. On sight the lesion carries 75 per cent diagnosis of syphilis. The other possibilities after three months are of course trichophytic sycosis, lupoid sycosis, sporotrichosis, actinomycosis.

The Wassermann reaction was strongly positive the therapeutic response immediate.

This patient could give no history of infection. He had at one time had "tuberculous symptoms, but no Wassermann test was available at that time.

DERMATOPHYTOSES (RINGWORMS) IN THE DIFFERENTIAL DIAGNOSIS OF LATE SYPHILIS

The annular configuration of many syphilids and especially of recurrent and late syphilids seems to have had a fatal effect on their diagnosis in the hands of the dermatologically untrained practitioner and the layman. The term "ringworm" perpetuates the idea that a circular or circinate lesion is of local parasitic origin, and has reduced the threshold of suspicion for syphilis. It is



Fig. 511.—A typical ringworm of the back of the neck. There are miliary vesicles in the margin and scaling with occasional minute pustules in the center. The border is palpable, but not indurated.

a better plan to regard ringed lesions as suspicious of syphilis and eliminate the graver possibility than to form a habit of dismissing arcs and circles as insignificant, or worthy only of local treatment and no observation.

Confusion with syphilis should seldom arise except in those forms of dermatophytic infection which involve the palms and soles and which produce circinate lesions on the face or body. The



Fig. 512.—A dermatophytosis of the trunk, showing the typical superficiality, the border, the scaling center, and the presence of satellite lesions in the surrounding normal skin producing the anomalous configuration. The organism was demonstrable in the scales.

Note the complete absence of atrophy and scarring even in a lesion of this extent. The progress of the process was much too rapid for a syphilid.

more severe forms of trichophytic infection, giving rise to fungous hypertrophic lesions, such as kerion, or to deep involvement of the bearded region with marked thickening and crusting with pus, abscesses and loss of hair from follicular pustulation do not in the least resemble syphilids as they have been here described. Dermatophytic processes in the skin are in general more acutely inflammatory and more rapidly progressive than syphilis.

Circinate dermatophytic lesions of the skin present a sharply defined border which is always less indurated than its width and height would lead one to expect of a corresponding syphilid.

The lesion is essentially above the surface of the skin and not below it, and this fact can be detected by the palpating finger



Fig 513.—Scarring produced by the infiltrative type of erythematous lupus, approaching sarcoid. The atrophic remains may suggest the scars of syphilid. Note the "chapping" of the lips. Follicular plugs, lesions about the ears, and bald scarred patches in the scalp help to clinch the diagnosis of erythematous lupus.



Fig 514.—The infiltrative or edematous border and arciform configuration with atrophic center occasionally seen in erythematous lupus. The blackish horny puncta near the lower eyelid and inner canthus are the epithelial plugs of this disease, though they need not be dark in color A hand lens is essential to the diagnosis of many cases of erythematous lupus.

The border of the dermatophytic lesion is scaling With the aid of low-power lens minut vesicles or vesicopustules can be detected, especially if the scale be lightly rubbed off That of the syphilid presents diff se translucence or nodular character but no vesicles or pustules.

Satellit lesions in the surrounding skin not continuous with the original lesion, and con-



Fig. 515.—Sarcoidosis of which the above is cutaneous lesion is clinical syndrome of tuberculoid character and is in fact believed by many observers to be an anergic nonconsenting type of tuberculosis with lesions in the lungs, bones, viscera, spleen, liver and so forth. The cutaneous lesions are characterized by lymphocytic infiltration of the corium with epithelioid cell proliferation and often giant-cell formation, whose histology may at times suggest either tuberculosis or gumma. Clinically they are bluish or brownish-red, slightly translucent, or at times almost colorless deep plaques, and intumescences, firm, fleshy and sometimes lobulated, occurring most often about the face. They may however appear as papules, nodules, or plaques on other parts of the body Transitions from erythematous lupus to sarcoid exist. In this case, observed over period of several years, and thoroughly studied from every angle, the transition from erythematous lupus through erythema elevatum diutinum to Boeck sarcoid could be watched. The sarcoid responds to the administration of arsenic, and hence to the prolonged administration of arsphenamine as in this case. This is sometimes the basis of error in diagnosis. Sarcoids rarely ulcerate, but the resemblance to nodular syphilid as here is sometimes very striking

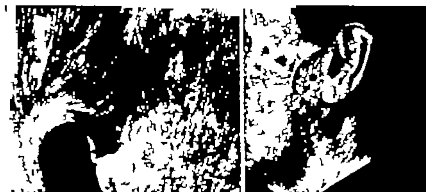


Fig. 516.—Basal-cell epitheliomas of superficial type with central healing and peripheral extension, somewhat suggestive of syphilids. The pearly border may not be recognizable, there may be cordlike induration and decision may be dependent on biopsy or on collateral evidence either for epithelioma (keratoses, etc.) or for syphilis. In doubtful cases with large or extending lesions it is safer to lean toward malignancy than toward syphilis in treatment, though investigation of the possibilities should be complete.

sequently anomalous configurations, are much commoner in dermatophytoses than syphilids. The center of a dermatophytic lesion is scaling and usually presents the lichenified appearance of dermatitis (Fig. 511) that of syphilid is wrinkled and atrophic, but there is little or no scale. The center of the dermatophytic lesion may present vesicles and vesicopustules which are absent in the syphilid.

Many dermatophytic lesions center around the hair follicles, and this fact may be detected both by the lens and by the ease with which hairs can be pulled out. In many cases the pustule is seen to have developed in the follicle mouth, its top pierced by hair. Dermatophytosis of hairy region shows a much more pronounced tendency t produce alopecia than do syphilids of hairy region, although an indurated syphilid may occasionally produce secondary alopecia, not so much from specific follicular localization of the lesion as from the general destructive effect of the diffuse infiltration.

Dermatophytic infections, with the exception of favus, d not tend to leave scars. It is remarkable how pyogenic and dermatophytic granuloma such as kerion can subside completely leaving the skin practically normal and the hair often intact or capable of complet restoration.

Whenever dermatophytic infection is suspected because of the superficiality the scaling, or the character of the border of lesion, an examination of scales and hairs for the causative organism must be made. The scraping should be thorough, but seldom deep enough to draw blood or lymph. The border is usually the richest in organisms. Scales and hairs, especially those which come out without effort, or which show deformity or softening of the shaft and papilla, should be soaked in 20 per cent potassium hydroxide solution for fifteen minutes to an hour until the keratin has softened, and then examined under high power for the mycelium and spores of the fungus.

LATE SYPHILIDS OF THE LIP AND MUCOUS MEMBRANES

The following types of late syphilids of the lip deserve special mention

1 Diffuse gummatous nonulcerative syphilid.

2. Ulcerative gummatous infiltration.

3 Solitary *gumma of the lip*

4 Nodular and nodulo-ulcerative late syphilids involving the lip and adjacent skin.

All of these types are here illustrated

Late syphilids of the mucous membranes occur in the following forms

1 Late recurrences presenting the arciform configuration and the nodular and ulcerative character of the nodulo-ulcerative syphilid of the skin.

2 Interstitial or sclerosing glossitis.

3 Fissure.

4 Solitary gumma.

5 Perforating gumma of the soft palate.

As late syphilis approaches the mucocutaneous junctions and invades the mucous membranes, a new risk, that of malignant degeneration makes its appearance. This malignant degeneration does not necessarily wait until the involution of the syphilid and the formation of a scar but may begin while the syphilid is still active and of comparatively recent development, and progress side by side with the syphilitic lesion, its presence unsuspected until glandular metastasis has occurred. For that reason it is highly important to inspect syphilids, especially ulcerative lesions on or near the mucous membranes, for the rolled or pearly border which suggests early epithelioma to search for lymphnodes at first examination to make microscopic examinations of tissue from suspicious lesions and to regard as suspicious and investigate microscopically all supposedly syphilitic lesions of the mucous membranes which do not make an immediate and complete response to the arsenicals and heavy metal. If for any reason such as the need for eliminating tuberculosis, slower methods of treatment than that with an arsenical must be employed it is better to take a specimen for examination first and treat afterward if

only inflammatory changes are found than to discover that a lesion is malignant after it fails to involute under several weeks of treatment. The metastasis of malignant lesions on the mucous membranes and mucocutaneous junctions is very rapid, and delay is exceedingly dangerous. The coexistence of a positive serologic reaction on the blood and a lesion on the lip or mucous membrane does not *ipso facto* prove the lesion to be a syphilid.

Because of their location, which often interferes with mastication and deglutition, late syphilids of the mucous membranes, especially of the tongue

Fig. 517

A SUMMARY OF THE CHARACTERISTICS OF LEUKOPLAKIA

A Grayish or Silvery Sharply Defined, Imbricated, Roughened, and Thickened Patch on mucous or mucocutaneous surface. A diffuse silvering of the mucosa, or stippling of silvery points, such is produced by lichen planus, is not the type of leukoplakia contemplated in this description.

On Finding Leukoplakia Look Backward Toward Syphilis, Forward Toward Cancer. Leukoplakia is not always of syphilitic origin, but it should always arouse strong suspicion of syphilis.

Irritation Alone Especially from T bacco and Bad Teeth, May Produce Leukoplakia, but irritation plus syphilis is even more effective. Syphilitics who use tobacco are especially subject to leukoplakia.

Leukoplakia also Occurs on the Penis and About the Mucous Surfaces of the Labia.

Syphilitic Leukoplakia is Scar—the scar of the mucous patch. It is not an active process, and it is useless to search it with the darkfield for *Spirochaeta pallida*.

Syphilitic Leukoplakia M y However Coexist with Fresh Mucous Patches, and with later gummatous manifestations on the mucous membranes. The surface of leukoplakia is drier tougher more leathery than mucous patch. It is not an easily removable pellicle or exudate.

In Conformity with the Sites of Predilection for Mucous Lesions, leukoplakia of the commissures of the mouth and the lip is most suggestive of syphilis. Next comes leukoplakia of the dorsum of the tongue, then of the anterior faucial pillars. Leukoplakia of the buccal and gingival mucosa is least suggestive of syphilis, and line of thickening along the junction of the teeth or slight buccal silvering is not suggestive at all.

A Wassermann Test is Not Sufficient to Eliminate th Possibility of Syphilis from patient presenting clinically suspicious type of leukoplakia. Look further even to the spinal fluid.

The Risk of Malignant Degeneration in All Forms of Leukoplakia is Serious. Destroy each patch with radium, cautery or excision as indicated.

A Leukoplakial Patch Which is Raised, has raised border or which is ulcerative or eroded may be already malignant. Excise such lesions and examine microscopically if possible in serial section before completing treatment or discharging the patient. Feel for glands.

Treatment for Syphilis Has N Effect on a Fully Developed Leukoplakia. Destructive measures are necessary part of its management whenever found.

Syphilitic Patients Should Give Up Smoking and practice rigid mouth hygiene if they show any tendency to relapse on the mucous surfaces, in order t reduce the tendency t develop leukoplakia.

and pharynx, may be associated with a grade of constitutional disturbance emaciation, and cachexia which is out of all proportion to their physical importance as lesions. Stokes has seen a starvation acidosis of a serious grade in a patient brought in as an ambulance case whose entire trouble was traceable to a crateriform ulcer of the posterior pharyngeal wall that was so painful that *swallowing had* become impossible.

Because of their location, and the associated constitutional condition, gummatous lesions of the posterior portion of the tongue, of the pharynx and nasopharynx and of the epiglottis are especially apt to be regarded as tuber

culous. This error is less likely to occur if the lesion is a typical solitary gummatous ulcer whose yellow base and raised or crateriform indolently inflammatory margin are comparatively easy to recognize. The arciform configuration of several confluent lesions may suggest their syphilitic character. Tuberculous ulcers are more ragged, usually more acutely inflammatory and



A B

Fig. 418.

TYPICAL APPEARANCE AND LOCALIZATION FOR SYPHILITIC LEUKOPLAKIA

Male, aged forty-one, married.

A, Commissural leukoplakia. Note the imbricated leathery appearance and the sharp contrast with the mucous membranes. The mucous patch shown in Fig. 412, A, is the commonest source of leukoplakial lesions of this type.

B, Labial leukoplakia the result of mucous lesions such as that in Fig. 412, B. This is typical smoker patch.

DISCUSSION

This patient came to the Section of Dermatology for "eczema of the hands" of fifteen years duration. He had not the slightest suspicion that he had syphilis, and could give no history of early manifestations, although he admitted two attacks of gonorrhea.

Immediately upon examining his mouth he was told that there was an 80 to 90 per cent probability that he had syphilis. The Wassermann reaction taken next day was strongly positive.

The eczema of the hands was at first supposed to be a palmar syphilid, but responded too slowly to treatment, and relapsed with typical fissuring in six months.

There was no definite history of mucous lesions obtainable. The patient did not seek relief for his leukoplakia. He was a moderate smoker of pipe and cigars.

There is no evidence of beginning malignant degeneration about these lesions. None the less they were treated with radium with completely satisfactory results.

It is not contended that all leukoplakia is syphilitic, but leukoplakia of the lips and commissures should invariably arouse suspicion and lead to a full investigation for syphilis. This patient could not be followed long enough to secure a spinal fluid examination, though there were clinical reasons for suspecting the need for it (early paresis (?))

painful, though not necessarily so, and are apt to present a characteristic of all tuberculous processes in that the margins are less sharply defined than those of syphilids, and minute reddish yellow translucent points beyond the edge of the ulcer indicate the sites of tubercles in the subjacent tissue which has not yet broken down. It is frequently possible to demonstrate tubercle

bacilli in smears from the floors of tuberculous lesions of the pharynx and tongue, and tuberculosis of these regions is seldom primary so that a focus can be found in the chest on physical examination.



Fig. 510

LEUKOPLAKIA OF THE DORSUM OF THE TONGUE IN A SYPHILITIC WHO COMPLAINED ONLY OF PSORIASIS

Male, aged forty-three, married.

This patient came to the clinic to seek relief for psoriasis and for a sore tongue. He had no idea that he had syphilis and seemed dazed when told before the blood Wassermann test was taken that the condition on the tongue was almost certainly syphilitic. Subsequently he showed in both speech and manner signs suggestive of early paresis. The neurologic examination, however, yielded nothing.

The Wassermann reaction on the blood was strongly positive. Spinal fluid Wassermann +++ with 0.4 and 1 c.c., Nonne positive, 60 small lymphocytes and 3 large lymphocytes, gold sol 4555543210.

The small ulcerative lesion and nodule did not respond to treatment for syphilis and were regarded as probably early epithelioma. Radium was used.

Note the destruction of the papillæ by the process which produced the leukoplakia. This destruction of the papillæ with an equal amount of scarring but without leukoplakia can be produced by syphilitic sclerosing glossitis which produces a smooth red shiny tongue (see Fig. 384).

This patient had had psoriasis for fourteen years. The leukoplakia of the tongue had first attracted his attention eighteen months before coming to the clinic. There was also some involvement of the angles of the mouth. On questioning, the patient recalled having had canker sores in this region for some years.

The canker sore (aphthous ulcer) is a familiar misinterpretation of the mucous patch.

In psoriasis occurring in conjunction with leukoplakia of the tongue leukoplakia is sometimes regarded as psoriasis of the tongue. The consensus of authoritative opinion is that true psoriasis of the mucous membranes is disputable.

Note the negative neurologic examination with so high a grade of cerebrospinal involvement.

The pathologic demonstration of malignant changes in a syphilid of the mucous membranes may call for more than one examination of tissue, inasmuch as the beginnings of a malignant degeneration may be missed in a single biopsy from an extensive lesion. In general, for tissue examination the piece

should be taken from the border which is *hardest* to the palpating finger To avoid the slightest risk of inducing traumatic metastasis, the biopsy should be taken on the operating table under conditions which permit immediate execution of any operative procedure which may be called for if a malignant degeneration is found



Fig 510

NON-SYPHILITIC LEUKOPLAKIA WITH COINCIDENT SECONDARY SYPHILIS

Male, aged twenty single, farm hand.

This leukoplakia was limited to the buccal mucosa of the left side of the mouth, and was the result of the chronic irritation of chewing tobacco. Nothing could be a better demonstration of the fact that syphilis even when present is not invariably the cause of leukoplakia.

This patient had a coincident florid secondary syphilis, too early to have been instrumental in the development of the leukoplakia.

It is interesting that no signs of a primary lesion could be found, but there was history of a bubo *below the right ramus of the jaw* which had been incised a year before A chronic inflammatory process in the skin about the scar suggested the possibility of actinomycosis, but the pathologic diagnosis of the excised gland was tuberculosis, and nothing could be obtained from the pus.

The patient according to his statement had been assured by a physician that the corymbose follicular and papular secondary syphilid was a drug eruption. The Wassermann reaction was strongly positive

The differentiation of gumma and tuberculosis by the examination of excised tissue from lesions in the mouth and throat involves a considerable factor of possible error Both lesions are histologically granulomata and the picture presented by the tissue in the absence of typical tubercles may make a reliable diagnosis of tuberculosis impossible. *In all such examinations, especially when carried out by a laboratory not in close touch with the clinician who excised the tissue the typical tubercle in sufficient numbers to place the diagnosis beyond question, or the finding of the bacilli is the only sound basis for a diagnosis*

of tuberculoma. In all other cases in which tuberculosis is suggested, but not established, a report of "Granuloma, uncertain etiology but probably tuberculous" is the conservative diagnosis. If plasma cells are present we believe it



Fig. 341

EARLY CARCINOMATOUS DEGENERATION LEUKOPLAKIA OF THE TONGUE. NO SYPHILIS DEMONSTRABLE

Female, aged forty-one, widow

Note the superficial ulcers.

The only significant physical findings were hypo-acidity and small fibroid uterus. Syphilis is, however, sometimes difficult to demonstrate by single examination in women.

A pathologic examination for malignancy should be secured on every leukoplakia which shows any *signs* of ulcerative or proliferative change.



Fig. 342.—Gummatous nonulcerative infiltration of the lower lip. Note the entire absence of ulceration. Lesions of this type may attain an almost wooden hardness. (Collection of Dr F. G. Harris.)

to be entirely within the province of the pathologist to suggest the possibility of a syphiloma, and entirely proper on the basis of such a report for a clinician to institute a therapeutic test for syphilis rather than an immediate operative intervention. *Ten to fifteen daily injections of mercury succinimide* (½ *grain*) *or*

should be taken from the border which is *hardest* to the palpating finger To avoid the slightest risk of inducing traumatic metastasis, the biopsy should be taken on the operating table under conditions which permit immediate execution of any operative procedure which may be called for if a malignant degeneration is found



Fig. 520

NON-SYPHILITIC LEUKOPLAKIA WITH COINCIDENT SECONDARY SYPHILIS

Male aged twenty single, farm hand.

This leukoplakia limited t the buccal mucosa of the left side of the mouth, and was the result of the chronic irrit tion of chewing tobacco. Nothing could be better demonstration of the fact that syphilis even when present is not invariably the cause of leukoplakia.

This patient had coincident florid secondary syphilis, too early to have been instrumental in the development of the leukoplakia.

It is interesting that no signs of primary lesion could be found, but there was a history of bubo below the right ramus of the jaw hich had been incised year before A chronic inflammatory process in the skin bout the scar suggested the possibility of actinomycosis, but the pathologic diagnosis of the excised gland was tuberculosis, and nothing could be obtained from the pus.

The patient according t his statement had been assured by physicia that the corymbose follicular nd papula secondary syphilid as a drug eruption. The Wassermann reaction w strongly positive

The differentiation of gumma and tuberculosis by the examination of excised tissue from lesions in the mouth and throat involves a considerable factor of possible error Both lesions are histologically granulomata and the picture presented by the tissue in the absence of typical tubercles may make a reliable diagnosis of tuberculosis impossible. *In all such examinations especially when carried out by a laboratory not in close touch with the clinician who excised the tissue the typical tubercle in sufficient numbers to place the diagnosis beyond question, or the finding of the bacilli, is the only sound basis for a diagnosis*



Fig. 381.

SUPERFICIAL SCLEROSING SYPHILITIC GLOSSITIS ("GLATTZUNGE")

Male, aged fifty-two, farmer

A Tongue Over Considerable Portion of Whose Surface the Papillæ Have Disappeared, or Whose Outlines or Surface are Distorted or Lobulated by Smooth Cicatricial Contractile Bands Should Arouse Strong Suspicion of Syphilis.

Note the smooth shiny atrophy of the left side of the tongue as compared with the normal "furry" surface on the right. The same smooth atrophy may involve the whole surface, or may be confined entirely to the portion of the tongue posterior to the circumvallate papillæ, where it can be felt rather than seen. The smoothness is the sequel of superficial gummatous infiltration which on involution leaves the atrophy. The active process often does not attract the patient's attention, or may be accompanied only by slight redness, or burning sensation on eating acid foods. This latter is a nondescript symptom that may occur with any form of glossitis and is not at all distinctive of syphilis.

Symmetric cross-striation of the tongue, which also occurs in this picture, is not evidence of the presence of syphilis unless produced by actual scar tissue. The congenital anomaly of "scrotal tongue" is sometimes confused with the scarred tongue of interstitial glossitis through failure to appreciate that there must be actual *scarring*, not merely furrow.

It was Suggested on Examination of This Patient, That All the Pathologic Change Might Be Ascribed to His Rather Heavy Use of Tobacco. None the less, an investigation for syphilis was made. The following was the result:

1. A penile lesion at nineteen years (thirty-three years ago).
2. Married twenty-four years, wife well, 4 children well, no miscarriages (married after the infectious period).
3. A negative blood Wassermann reaction, negative on one repetition, **But Once Positive and With One "Clears Slowly" in 6 Tests Following Provocative Injection.**
4. A negative spinal fluid, but definitely irregular pupils and marked reduction of bone fork sensation.

Whether Tobacco is a Factor or Not, It Is Worth While to Investigate Syphilis in Patients with Tongues Like This. This Patient had Syphilis Albeit the Infection was a Mild One.



FIG 525 —SCLEROSING GLOSSITIS OF THE DEEP OR INTERSTITIAL TYPE

This type of lesion produces lobulation of the margin of the tongue after the process subsides. Deep gummas likewise produce cicatricial contracture (Collection of Dr F G Harris)



A B

FIG. 526 —SYPHILITIC SCLEROSING GLOSSITIS LIMITED BY LICHEN PLANUS OF THE TONGUE.

In B is shown the reticulation and stippling of the buccal mucosa of the same patient which is characteristic of lichen planus. It seems trit t suggest it, but no lesion on the tongue should be diagnosed without an examination of the mouth and of the skin.



FIG 527

FACTITIAL GLOSSITIS IN BENIGN PLAQUE OF THE TONGUE

A Patch of Smooth Atrophy of the Tongue is Not Pathognomonic of Syphilis.

T the right of the midline on the dorsum of the tongue is patch the size of penny exhibiting not only loss of papillæ but tual superficial scarring with leukoplakia.

On the left-hand margin of the tongue i thick bit plaque one of t lesions originally present constituting the condition known benign plaques of the tongue

On First Sight Tongue Like This Would Appear to be Worth 85 Per Cent. for Syphilis. The patient uncommunicative and it w not until an in estigation for syphilis w begun that found that she had been treating whitish patches, under the instructions of physician, ith nitrat of sil er f r some months. This systematic cauterization in all probabil ty responsible for the destruction of papillæ and the scarring The plaque on the left margi almost too smooth, whit and thick for typical syphilitic leukoplakia

Darkfield and culture of both lesions w entirel negative

The patient had married t t enty-one years of age A full in estigation for syphilis as entirely negative. The leukoplakial patches ere treated ith radium.

The bacteriological examination of lesions on the mucous membranes by smear and darkfield involves important elements of error which the syphilologist must take into account. The finding of tubercle bacilli in smears as an

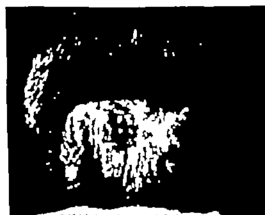


Fig. 528.—The Typical "Leukoplakia" of Lichen Planus upon the So-called "Scrotal Tongue," a Congenital Abnormality.

The term "leukoplakia" is a misnomer in lichen planus, for the lesion disappears under treatment for the general condition, as do the lichen planus papules on the skin. Remember that lichen planus clears up under both mercury and arsenic.

aid to the identification of tuberculous lesions has been mentioned. In common with all destructive lesions in the mouth, ulcerating late syphilids present a rich saprophytic flora. The Vincent symbiosis of a large spirillum and a fusiform bacillus (variations on a common type form) may be abundant in the



Fig. 529.—Periadenitis Mucosa Necrotica Recurrens of the Tongue.

This is probably an infection of the mucous glands, which may clear up under arsphenamine. This patient had had repeated acute attacks.

necrotic tissue of histologically demonstrated epithelioma and lymphoma, and there seems no intrinsic reason why, as on the genitalia, such a combination should not occasionally be found in the necrotic tissue of gummas. While we have no demonstrative evidence to offer on this point as yet, we believe that



Fig. 533.

PERFORATING GUMMA OF THE SOFT PALATE

Male, ged forty-five single, railroad man.

Perfor tion of the Hard or Soft Palate Is th Nearest Approach to Pathognomonic Sign of Syphilis to be Found on th Mucous M mbranes.

While epithelioma and Vincent angina may occasionally ca se destructive changes in these regions, perforation which does not show marked neoplastic change in gross examination is almost invariably syphilitic in origin. The active lesion is often surprisingly *inconspicuous and painless. A slightly edematous margin to the opening* may be the only evidence of activity in rapidly progressing process. W th marked involvement of bone the fetor is very pronounced.

This Patient was Wassermann Negative on th Blood, and Had Been So on Several Occasions Before Entering the Clinic. Gummas f the Hard and Soft Palate are Not Infrequently Wassermann Negative This patient syphilitic infection wa of t only eight years duration and ulcerative processes in the palat nd pharynx had begun fifteen years after onset At that time the patient received arsphenamin, the lesion healed, and he discharged as cured

Two Attempts Had Been M de to Close th Supposedly Healed Perforation by Plastic Operation, both of hich failed completely the lesion breaking dow ithin ten days The second ttempt as made following 3 arsphenamin injections and 11 injections of mercury succinimid.

It is Saf Principle to Defer Operative Interfer nc with Palatal Syphilis Even in Wassermann N gativ Cases Until Months and Years of Intensive Treatment Have Been Carried Out. These patients al ys consider relief from the annoyance of the fistula first, and their eagerness for operation occasionally lead surgeons int interfering gainst their better judgment

The Mer Fact of Wassermann Negativity Means Littl or Nothing in th Diagnosis of Syphilis from Palatal Perforations. It is Also Not Saf Guide to Fitness for Operation.

Operative interference in syphilitic nasopharynx may cause violent flare-up of gummatous process which will cause tremendous destruction before it can be checked.

diagnoses of Vincent's angina should be made with much more reserve than in the past, in late as well as early syphilis, and that the morphology of the lesion and the collateral evidence for or against syphilis quite outweigh the bacteriological findings.

Darkfield examination for Spirochaeta pallida, while of the utmost importance in early and recurrent syphilis, is useless in late lesions of the mucous membranes.

LATE SYPHILIDS OF THE PALMS

Late syphilids of the palms are not infrequently symmetric and practically never ulcerate. For that reason border configuration, induration, and atrophy are the most significant characteristics in differential diagnosis. The morphological differentiation of palmar syphilis may be a matter of the greatest difficulty. Even an almost invincible suspicion in a given case may remain



Fig. 434.—Acute eczematous processes involving the palm are, as a rule, easy to identify because of their vesicular character. Chronic eczema, in which the acute inflammatory process has been replaced by scaling, fissuring, and thickening, is the type which is apt to be confused with a syphilid.

Vesicles in palmar eczema and dermatophytosis may be small, translucent and deep, or visible only as slight, apparently papular elevations. On puncture fluid exudes. Often they may be found along the sides of the fingers, though absent elsewhere. They may contain pus, and show a tendency to confluence, with extensive undermining, producing the so-called dermatitis repens.

Fissuring is the hallmark of chronic palmar eczema. Note the fissuring in these palms.

Syphilids, even of long standing, seldom fissure. If the patient gives a history of cracking of the affected skin during the winter, which may be the only season at which this phenomenon occurs, a diagnosis of syphilis must be made with the greatest caution.

Not all eczema of the palms produces fissures, however.

Eczematous changes in the palm may range from a smooth patch of thickened skin in the hollow of the hand to plaques, patches and gyrate lines, and groups of papules involving most of the surface. The tendency to involve the interdigital spaces is marked in eczema, and eczema exhibits a distinctly greater tendency to bilateral symmetry as regards the situation and shape of individual lesions than does syphilis.

In subacute eczema moist or oozing lesions may occasionally be found in the interdigital folds when all the rest of the eruption is dry. The finding of an oozing patch means that vesicles have been present and speaks against a syphilid.

Fig 535

IMPORTANT POINTS IN THE DIAGNOSIS OF PALMAR SYPHILIDS

1 The patient usually comes with a diagnosis of eczema.

2. Never be content with an examination confined to the local lesion. Insist on seeing all parts of the body

3 Look t the backs of the hands well the palms, and at the interdigital spaces, wrists, forearms, and flexures. The clue t the whole situation may lie in the finding of vesicles or indurated border in lesions in these places.

4 Vesicles eliminat syphilis for all practical purposes in adults. This does not mea that the patient may not have coincident syphilis, or palmar syphilid ith coincident eczema.

5 An indurated cord-like border suggests syphilid.

6. Take careful nd detailed history ith special reference t ( ) familial occurrence of the condition and (b) vesiculation t some earlier stage or previous outbreak of the eruption, ( ) itching, and increased irritation by w ter nd soap.

7 Study the nails. Look especially for psoriatic pitting

8. Take scraping if even the slightest scale can be raised on the lesion, and after soaking the scales for hour on slide in drop or two of 20 per cent potassium hy droxid, examine for trichophyton spores and mycelium, even though there be other evidence of syphilis. It takes familiarity and practice for this test.

9. The response of palmar syphilids t mercury has been slow in my experience, but rapid to arsphenamin and fairly rapid t bismuth.

10. If provocative procedure is carried out, see the patient daily for eek. If by the end of that time the lesion is not more than half involuted, better be cautious in basing diagnosis on the palmar lesion without supporting evidence.

11 Call an expert, and do not dismiss doubtful cases without rranging for observation and reconsideration.



Fig. 536.—This figure presents fairly good example of the diffuse erythematous syphilid of the palm which is most often regarded eczematous. The entire palm is red, rather doughy and infiltrated, perfectly dry and moderately scaling. Here and there suggestions of mottling or spotting with slight trophic changes can be recognized, especially where the skin is normally thinner as at the base of the thumb. Th border is the crux of the whol matter Note the sharp raised margin along the wrist and the index finger On palpation distinct cordlike subcuticular resistance could be felt in the margin which wa distinct from the "feel" of the rest of the eruption. The left palm wa involved, but less extensively tha the right.

wholly unconfirmed while the ability of a palmar syphilid to simulate other dermatoses is so perfect that the most expert may be thrown wholly off his guard. The inexperienced should be quick to suspect, slow to diagnose palmar syphilids.

The ubiquity of ringworm infections of the palms and soles is little realized. Halsey and Jordan found 67 per cent of 100 students to present clinical lesions, 5 per cent culturally demonstrable and 15 per cent with definite histories of previous attacks. The ringworm of the palm is



Fig. 537

THE MORPHOLOGIC DIAGNOSIS OF A WASSERMANN NEGATIVE PALMAR SYPHILID

Late syphilids induce permanent changes in the skin which they involve. On the palm, *atrophy rather than scarring is the expression of this change.* Atrophy shows itself as a loss of substance in the cutis without destruction of the overlying epidermis. The epidermis collapses into the shrunken base, and is both thinned and flattened in the process which leads to the atrophy. The predilection of syphilis for destruction of the elastica, plus the shrinkage of the base and the thinning and flattening of the epidermis, leads to the wrinkling which occurs in the skin that has been involved by a syphilid. **On the Palm this Atrophy Appears as Wrinkling and Thinning—an Aging of the Palm. Eczema, It Should Be Remembered, Produces Thickening of the Palm.**

Why Has This Young Woman a Syphilid and Not an Eczema of the Palm, she and her physician thought she had

1. *Note the Border.* It was distinctly cord-like, of a dull brownish-pink color. The induration was distinctly palpable. The entire process was dry.

2. *Note the Atrophy.* On one side of the dividing line of induration (toward the wrist) is the smooth, elastic, pink "rubbery" texture of the skin of a young woman. On the other side of the border is the thinned, flaccid, wrinkled, atrophic skin of an old woman, plus the faintest trace of hyperpigmentation. There is twenty years' difference between the two parts of the palm, produced by the passage of the line of induration across the surface.

3. The lesion was unilateral. There was slight involvement of the backs of the fingers, each lesion with a definite border.

4. There were no fissures or vesicles or history of either, no eczema elsewhere, no family history.

1

Fig. 537.—Continued.

5. **The Blood Wassermann Reaction was Negative** but in the presence of a lesion so definitely conforming to the morphologic characters of palmar syphilid, this does not exclude syphilis.

6. In the diagnosis of a lesion of this sort, in which syphilis is denied by the patient and not supported by the positive blood Wassermann reaction, two other aids to diagnosis may be drawn. A provocative procedure, it will be recalled, provides the opportunity to watch for a focal flare-up after the arsphenamin injection, and constitutes a short therapeutic test. A provocative test was done in this case.

7. No positive Wassermann reaction could be obtained following three decigrams of arsphenamin intravenously but the **Lesion Underwent a Marked Focal Flare-up During the Twenty-four Hours Following the Injection. It Then Subsided, and by the End of the Seventh Day had Practically Vanished.** An attempt was made to photograph this flare-up, and the sharper definition of the border and the presence of points of activity not visible in the lesion before injection could be made out by close inspection in spite of the difficulty in recording the color values. The whole palm showed a distinctly deeper blush, as well as the border.

Discussion

No positive Wassermann test on the blood has ever been obtained from this patient in five years of observation. She was forty years of age at the time the lesion was first seen, and had been married at thirty-two years of age. Her husband, apart from a duodenal ulcer, enjoyed good health. There had been no pregnancies, though no preventive measures had been used. A chronic salpingitis was found at a subsequent operation. The patient's denial of infection was made in good faith, though error might have crept into some of the collateral anamnesis. No other evidence of syphilis than the palmar lesion could be elicited in a complete examination.

The Lesions Vanished with the First Arsphenamin Injection, and Have Never Reappeared. No ringworm could be found in the scales.

Is it Justifiable to Make a Diagnosis of Syphilis on the Basis of the Palmar Lesion Here Shown, in Spite of Repeatedly Negative Wassermann Reactions and Negative General, Neurologic, and Special Examinations Including a Negative Spinal Fluid?

We Believe That it is. A Persistently Negative Blood Wassermann reaction is not a rare finding where the diagnosis of syphilis can be established beyond peradventure. It is entirely compatible with the development of active syphilids in the skin.

Syphilis in Women Runs a Traditionally Mild Course. Solitary manifestations are quite in keeping with this characteristic.

Had there been no Herxheimer flare-up, had it taken three weeks to clear up this lesion instead of one, or had she had recurrences, the diagnosis would have been in doubt. The arsenic in arsphenamin might clear up a palmar eczema if the drug were continued. The ideal procedure, had time permitted, would have been to clear up the lesion with mercurial treatment (mercury succinimid intramuscularly ⅕ grain daily).

In a Woman Within the Childbearing Age It is Sometimes Advisable to Treat "For Life Insurance" Provided It is Carefully Done Even When the Evidence of Syphilis is Less Suggestive than This. It May be Accepted as Axiomatic that Women in Whom the Suspicion of Syphilis Has Been Raised on Reasonable Grounds Should Have the Benefit of Observation at Intervals for Some Years.

best identified by its associations, though these do not, of course, eliminate syphilis. The associates of palmar ringworm are (1) the soft corn and fissure between the toes; (2) the eczematous extension from fissure with the oozing, furiously itchy patch of dermatitis on the palmar surface; and the hyperkeratotic-vesicular ringworm, in which vesiculation occurs only occasionally the lesion usually as here being keratotic plaques. At times this keratosis may be so marked as to constitute veritable armor as in the keratodermic ringworm of the heel, which should not be confused with the keratodermic syphilid. Examination of scales, while important, is less often conclusively diagnostic than are the clinical considerations.



Fig. 534.

(For accompanying text description see next page.)

Fig. 538.—*Continued.*

THE DIAGNOSTIC PROBLEM OF A PALMAR SYPHILID

Mrs. A. B., aged twenty-eight, married, husband a railroad man, sought relief for "ringworm of the hand" and incidentally was seeking opinion on the advisability of bringing suit for x-ray burn of the right palm. Three years ago circles had appeared on both palms simultaneously. A practitioner with x-ray equipment had told her, according to her story, that she had "ringworm" and had made six exposures in eight days. Later she had consulted a dermatologist of competence who had made a diagnosis of psoriasis, she said. From her description she had then apparently been given Fowler solution.

The two palms confirm the treatment story and illustrate graphically two of the most serious potential errors in the morphologic diagnosis of all cutaneous recurrent and late syphilis, but especially of palmar lesions.

The right palm exhibited the scarred, telangiectatic, and fissured surface of a typical x-ray dermatitis.

On the left wrist was an active lesion of the type which had led to the previous diagnoses. The ring was almost perfect, with a ribbon-like band of slight induration and the faintest appreciable scale. The center was fawn colored, smooth, slightly wrinkled, and atrophic.

The left palm was thickened and hard, and studded with typical small arsenical keratoses.

Why Suspect Syphilis?

1. An indurated, perfect circle with slight but definite central atrophy and almost no scale.

2. Not a vesicle in the margin or elsewhere. Too much induration, too narrow and perfect a band, too exquisite a definition, no organisms in the scales.

3. With the above considerations not a sign of psoriasis on the nails or elsewhere on the body.

The Wassermann Reaction was Positive. The lesion practically disappeared before the second arsphenamine injection. A positive Wassermann reaction was obtained later elsewhere. There has never been a recurrence in three years' observation. The history of infection was negative except for one spontaneous miscarriage at three months, no subsequent pregnancies.

If the Wassermann Test had Been Negative? It Should Be Repeated and if Persistently Negative the Therapeutic Test and Subsequent Observation as Outlined Would Have Established the Case. A lesion that would not yield to arsenic enough to produce keratoses would hardly yield to the arsenical effect of one injection of arsphenamine. But it is well to be cautious in drawing conclusions from arsphenamine therapeutic tests, especially in palmar lesions.



Fig. 539.—The hyperkeratotic ringworm of the palm. Fungus found in the scrapings

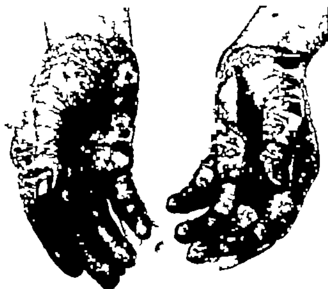


Fig 540.—An example of probable psoriasis of the palms. The geographic configurations are at times quite suggestive of syphilid. The complete lack of induration, lesions of psoriasis elsewhere (sometimes absent), the psoriatic changes in the nails (Fig 530), and the elimination of syphilis by lack of collateral evidence make the diagnosis. At times lesions of both these types are produced by ringworm fungi, and the scales should, accordingly be routinely examined.



Fig. 541

The syphilologically suspicious mind will see at once in the group of lesions on the thenar eminence a suggestively arciform configuration. The individual elements are dense, almost translucent horny papules with the faintest suggestion of pink in the tissue about the base and a central dell or crater not unlike that of a large arsenical keratosis (see Fig. 293) or the pit that *remains when the necrotic plug is extracted from* a papulonecrotic tuberculid lesion. The differentiation is given in connection with Fig. 542.

This is "laes cornée" of the palm. On the heel, where the general hyperkeratosis is more marked, the lesion is less conspicuous and may simply appear as pits i[illegible] thickened integument.

The History of This Case is as Follows:

A robust young married woman of t[illegible]enty-eight presented herself [illegible]ith [illegible] complaint of obstinate and persistent headache and backache. I[illegible] the course of her general examination the lesions show[illegible] [illegible]bove [illegible]ere recognized by her general examiner and described as looking "like corns on the fingers. The dermatologic floor consultant was [illegible]sked t[illegible] see the [illegible]arts. There [illegible]ere no other cutaneous lesions. The general examination had disclosed signs of chronic salpingitis, the eyes [illegible]ere negative and [illegible] sacro-iliac belt wa[illegible] suggested for relief of her symptoms.

Th[illegible] Blood Wassermann Reaction was Negative on Four Repetitions. The spinal fluid examination yielded the following findings: WR negative 0.4 and 1 cc [illegible]onne positive, lymphocytes 152, gold sol 4553202000. **Even with This Spinal Fluid th[illegible] Neurologic Examination was Negative.**

In the first taking of this patient [illegible] history she gave no information regarding her husband, but in subsequently discussing the matter with her husband it developed that she had separated from him [illegible]t one time and then returned t[illegible] him, that she knew he had syphilis and had been treated for it, but supposed he [illegible]as cured The subsequent examination of the husband revealed the lesions show[illegible] in Fig 414.

The larger part of this patient [illegible] symptoms were due to the high-grade meningeal neurosyphilis which she presented, and were markedly improved by treatment. **It is Worth Remembering that There is Not [illegible] Singl[illegible] Phase of Active as Well as Latent Syphilis Which Cannot Occur in Association with [illegible] R[illegible]peatedly N[illegible]gative Blood Wassermann Reaction. Only [illegible] Spinal Fluid Examination Will Disclose the Real Status of Many Cases with Neurasthenia or Indefinitely Explainable Constitutional Complaints.**



Fig. 542.—The Papulonecrotic Tuberculid of the Fingers (Folliclis)

A, Note the small brownish-black plugs and the occasional conical pits in the skin of the index-fingers. In the middle finger is a papule with a central depression not unlike that on the index-finger of the patient in Fig. 541. This is the papulonecrotic tuberculid of the hands, known technically as "folliclis."

B, Note the characteristic scarring produced by the tuberculid on the dorsums of the fingers, and active lesions on the index and middle fingers.

The Individual Lesion of the Papulonecrotic Tuberculid of the Finger Runs the Following Characteristic Course. It begins as a tender point, at which a papule forms, in the center of which a vesicle appears. The vesicle becomes dark and dries down, leaving a papule with a central conical plug which is the elementary lesion of the papulonecrotic tuberculid wherever it occurs. This plug can be picked out as the lesion heals, leaving a central conical depression which flattens in time to a small round white atrophic scar.

The Lesions Usually Appear in Crops, and the patient can often give a definite history of the vesicular stage and of the pain on pressure which resembles "a thorn sticking into the flesh." The sites of predilection are *the fingers, not the palms*, and especially the tips and the backs of the fingers. The scars can usually be found on the back of the fingers as in A, which also presents one or two active lesions. The fingers are apt to show some vasomotor disturbance in folliclis, and to be cyanotic, cold, and clammy. **The Tuberculid Has No Distinctive Configuration Such as That Usually Found in Syphilids.** The scattered character of the lesions is apparent from the scars as well as the active lesions. There is some tendency to localize at points of trauma.

A fairly rapid evolution (two weeks), showers or crops, repeated often in a seasonal manner (spring and fall), the history of vesiculation and tenderness, all of which contrast with the course of a syphilid, and the lack of configuration, the localization to the finger tips and backs of the fingers, and the formation of the characteristic small round white scar distinguish folliclis from a syphilid. In addition, there may be tuberculid lesions in other parts of the body, especially the forearms and elbows, and the legs. **The Importance of This Differentiation May be Appreciated from the Fact That Patients with Tuberculids May Have Partial Positive Wassermann Reactions on the Blood from Time to Time.**



Fig. 541

The syphilologically suspicious mind will see at once in the group of lesions on the thenar eminence a suggestively arciform configuration. The individual elements are dense, almost translucent horny papules with the faintest suggestion of pink in the tissue about the base and a central dell or crater not unlike that of a large arsenical keratosis (see Fig. 293) or the pit that remains when the necrotic plug is extracted from a papulonecrotic tuberculid lesion. The differentiation is given in connection with Fig. 548.

This is "lues cornée" of the palm. On the heel, where the general hyperkeratosis is more marked, the lesion is less conspicuous and may simply appear as pits in thickened integument.

The History of This Case is as Follows:

A robust young married woman of twenty-eight presented herself with a complaint of obstinate and persistent headache and backache. In the course of her general examination the lesions shown above were recognized by her general examiner and described as looking "like corns on the fingers." The dermatologic floor consultant was asked to see the "warts." There were no other cutaneous lesions. The general examination had disclosed signs of chronic salpingitis, the eyes were negative and a sacro-iliac belt was suggested for relief of her symptoms.

The Blood Wassermann Reaction was Negative on Four Repetitions. The spinal fluid examination yielded the following findings: WR negative 0.4 and 1 cc., Nonne positive, lymphocytes 152, gold sol 4333202000. **Even with This Spinal Fluid the Neurologic Examination was Negative.**

In the first taking of this patient's history she gave no information regarding her husband, but in subsequently discussing the matter with her husband it developed that she had separated from him at one time and then returned to him, that she knew he had syphilis and had been treated for it, but supposed he was cured. The subsequent examination of the husband revealed the lesion shown in Fig. 411.

The larger part of this patient's symptoms were due to the high-grade meningeal neurosyphilis which she presented, and were markedly improved by treatment. **It is Worth Remembering that There is Not a Single Phase of Active as Well as Latent Syphilis Which Cannot Occur in Association with a Repeatedly Negative Blood Wassermann Reaction. Only a Spinal Fluid Examination Will Disclose the Real Status of Many Cases with Neurasthenia or Indefinitely Explainable Constitutional Complaints.**

Syphilitic changes in the nails are in general, not particularly distinctive. The principal point upon which diagnosis may rest is not so much changes in the nail itself *as the association of paronychia and dactylitis of the terminal phalanx with the nail pathology.* Taken as they stand,



Fig. 545.—Lesions of the Nail and Nail Bed.

eczema of the nails, dermatophytosis of the nails, and trophic changes induced by syphilitic paronychia may at times be absolutely indistinguishable. Even the paronychia is not particularly distinctive.



Fig. 546.—The so-called "symmetric spade nail" or spoon nail, proposed by Varney as sign of syphilis. This patient had syphilis, and had sustained an operation for syphilitic gastric symptoms before coming to the clinic.

In the case here presented the friability and destruction of the nail may be quite as well due to dermatophytic infection as anything else. More commonly however the ringworm nail is thickened, friable, and raised from its bed. A suspicion of syphilis was aroused in this case by the very marked paronychia with thickening of the entire tip of the finger. The patient ad-

mitted having had genital sore fifteen months before and having been treated by intramuscular injections at the time his secondary eruption appeared. The trouble with the nails was of three months duration. *The blood Wassermann reaction was negative On provocative injection of arsphen-*

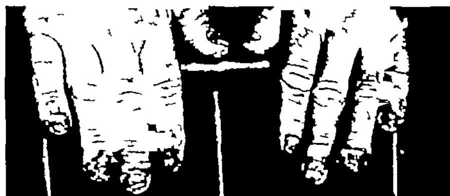


Fig 547 —Syphilitic onychia. Note the paronychial changes. (Collection of Dr William Allen Pusey)

amine however two moderately positive, one weakly positive one negative and two strongly positive tests were observed in six successive days. A well-defined local reaction (Herxheimer) with pain and tenderness followed the first arsphenamine injection. Marked improvement followed with the



Fig 548 —Tuberculosis may produce dactylitis and paronychia simulating syphilis, as well as collateral changes in the nail suggestive of trichophytosis. It is not necessary that all the nails be involved to suggest a systemic origin. In this case there was marked associated paronychia wherever the nail was involved. The nail of the right middle finger strongly suggests beginning trichophytosis. The tuberculous nature of the process was determined by biopsy from the left little finger and syphilis excluded by full investigation. The patient died of mesenteric tuberculosis two years later

institution of treatment. The paronychia disappeared, but the nails did not become completely normal even after three courses.

No dermatophytic organism could be demonstrated in scrapings from the nail but it is difficult to get positive findings in these cases



Fig. 549.—Dermatophytic nails. Note the thickening and elevation of the nail from its bed. One or all of the nails may be involved, and the process need not be symmetric. The demonstration of the fungus is best made by deep curettings from under the nail after prolonged maceration in 20 per cent sodium hydroxide on the slide.



Fig. 550.—Eczematous paronychia. Pyogenic organisms may be responsible for pictures ranging from this mild type to extensive and severe paronychial abscesses, and chronic exfoliative dermatitis of the finger ends (acrodermatitis perstans of Hallopeau). The pyogenic and impetiginous character and the greater acuteness of the inflammatory process in the nonsyphilitic conditions assist in differentiation.

MISCELLANEOUS CONDITIONS REQUIRING DIFFERENTIATION FROM LATE SYPHILIDS

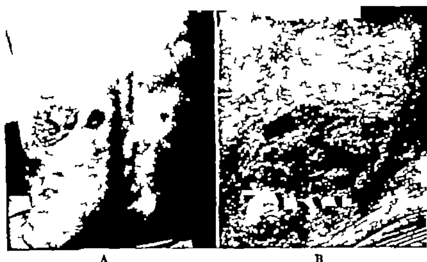


FIG. 551.—LYMPHOGRANULOMATOUS INFILTRATIONS OF THE SKIN SUGGESTING LATE SYPHILIDS, IN A PATIENT WITH HODGKIN' DISEASE.

The infiltrations are fleshy and indurated, and upon involution leave superficial atrophic scars with pigmentation, suggesting those of syphilids. There was no evidence of syphilis clinically or at autopsy



Fig. 552.—Arciform nodular infiltrations on the back of the hands, resembling syphilids, in Hodgkin disease. (Same case as Fig 551.)



A B

FIG. 453.—EARLY MYCOTIC STAGE OF M. CORIS FUNGOIDES.

The general dermatitis on which the syphilid-like infiltrations are beginning is shown in A. In B an early annular infiltrate is shown. These infiltrates are lymphogranulomas, fleshy and indurated, which on ulceration or spontaneous involution often leave pigmentation and atrophic remains very suggestive of syphilids. The infiltration of the face may suggest syphilid or lepra.

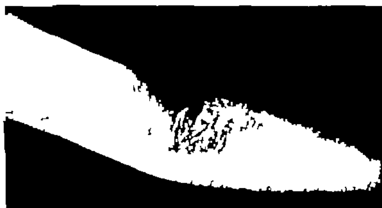


FIG. 454.—THE PAPULONECROTIC TUBERCULID ON THE ELBOW

This is one of the favorite localizations of this condition. Note the active dry necrotic-centered lesion among the scars. Compare this scar with that of the syphilid in Fig. 434. The crux in diagnosis hinges on the finding of typical papulonecrotic lesions, whether on face, hands, forearms, or legs. (See Fig. 348 for the hands of this patient.)



A B

Fig. 455.—This shows the remarkable resemblance that may exist between syphilids and tuberculids. The forearm in A shows crop of scattered late papules associated with an arciform lesion on the other arm, an aortitis, and positive blood Wassermann. Not that there are no scars, practically all the lesions being active papules without necrotic centers. I B, on the other hand, the proportion of scars as compared with active lesions is very large, and there are only few dry necrotic-centered papules. Arsphenamine therapy clears up both the tuberculid and the syphilid. The patient in B had been told he had psoriasis, the informant forgetting that psoriasis does not leave scars.



A B

Fig. 456.—Typical Lesions of Erythema Induratum Form of Tuberculosis of the Skin of the Leg

A shows the bluish-red infiltrated slightly softened plaque and B the symmetric distribution (not invariable) of the process. Not the papulonecrotic lesions adjacent t the large plaque. Erythema induratum usually occurs in women.



Fig. 487.—Scarring of tuberculids on the legs. Many of the scars in A have the configuration and peripheral pigmentation and the noncontractile atrophic character of syphilitic scars. Others, however show the scattering and lack of configuration which marks the tuberculid, as shown in B. Yet the scars in B could be mistaken for the scars of rupia, although rupia tends to appear on the trunk and face, tuberculids on the extremities. Both these patients were observed over considerable periods and the diagnoses completely verified.



FIG. 488.—THE EXAGGERATION OF TUBERCULOSIS BY SYPHILIS, PRODUCING TUBERCULO-GUMMATOUS SYNDROME.

This young woman had positive blood Wassermann reaction, and both parents had syphilis. She presents what appear to be broken-down tuberculous nodes, present since childhood (Vignolo-Lutati syndrome) and markedly indurated and extensive erythema induratum of the calf of the leg. Recovery under arsphenamine and mercury



Fig 559



Fig 560.

Fig 559.—Tuberculous gumma or gummatous tuberculosis (?) in woman with both tuberculosis and syphilis. The cervical glands were tuberculous, the blood Wassermann strongly and repeatedly positive Not the massive central slough and the involvement of the epitrochlear lymph node. Healing was rapid under combined treatment.

Fig 560.—Nodal tuberculosis of the fascia. This is a deep indurative form of tuberculosis, occasionally ulcerative, which may be mistaken for deep gumma. This young woman did not have syphilis, but made a rapid recovery under arsphenamine. Wende nodular tuberculosis of the hypoderm, hich does not ulcerate, ill also respond t arsphenamine.



Fig. 561.—Lupus Vulgaris Erythema forms

A form of cutaneous tuberculosis which may be confused with syphilis, dry type of great chronicity with some tendency to spontaneous healing. Not the entire lack of configuration suggesting syphilis, though this is not an invariable characteristic. Apple-jelly nodules may be identified Atrophic scars re visible



Fig. 502.—Tuberculosis Verrucosa Cutis.

The lesion is annular in configuration, but with typical verrucous papillomatous border



Fig 503 —Cutaneous extensions of tuberculosis (tuberculosis verrucosa cutis) from sinus opening in case of probable mediastinal tuberculosis. The scar is remarkably suggestive of that of late syphilid, and the active process was not clinically typical of tuberculosis. In attempting to make diagnosis of such lesion by examination of excised tissue, it should be remembered that tuberculosis verrucosa cutis does not invariably present typical tubercles. The scar suggests that of blastomycosis. There was slight temporary response to treatment for syphilis. The blood Wassermann reaction was negative.



Fig. 504.—A Typical Form of Sporotrichosis from Cutaneous Inoculation.

The site of inoculation is shown on the index finger Sporotrichosis of this type follows the lymphatics. The lesion on the finger is often spoken of as the sporotrichotic chancre, term which serves no useful purpose, and could well be discarded. Cultures can best be obtained from softened nodules before they discharge.

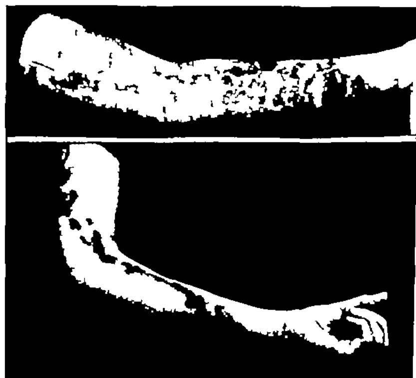


Fig 563 —A classical lymphatic distribution in sporotrichosis, showing incidentally the value of cleaning lesion before ttempting a diagnosis. Every nodule had been incised without decision. There is no object in ttempting histologic diagnosis of sporotrichosis from tissue for the picture is not specific.

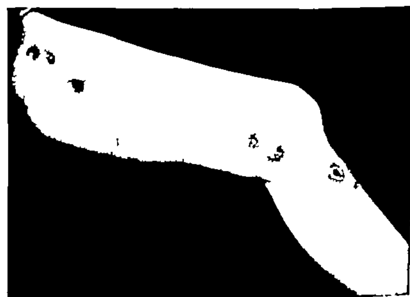


Fig 564.—Scattered sporotrichotic nodules suggesting rupial syphilitic lesions, but following the course of the lymphatics from the toe t the groin. They healed under arsphenamine and iodides.



FIG. 467.—BLASTOMYCOSIS OF THE LEG.

While the configuration may suggest syphilid, the papillomatous border eliminates it. The blastomycet was unusually abundant in the pus from the epithelial abscesses in this case.



FIG. 468.—THE IMITATION OF LATE SYPHILIDS BY BROMODERMA

The internal administration of bromides gives rise in hypersusceptible persons to pustular eruptions resembling acne (bromide acne) and to fungus papillomatous and granulomatous lesions which may occasionally suggest syphilids. Like syphilid, the fungoid bromoderma may extend peripherally involuting centrally with the formation of thin and usually somewhat crusted or scaling area of slight atrophy. The border however is papillomatous and papillomatous border practically eliminates syphilis.

This is bromoderma with papillomatous border, extending peripherally and involuting centrally with the formation of thin slightly scaling somewhat hyperpigmented scar



Fig. 569.—Fungous or hypertrophic tuberculosis in the groin, momentarily suggesting large condylomas. There were typical lesions of verrucous tuberculosis elsewhere.



Fig. 570.—Syphilids are rarely vegetative or fungous in character. The so-called frambesiform syphilid is recognized, however. (Collection of Dr. Udo J. Wile.) The decision as to the syphilitic character of the lesion must rest on collateral factors. In the groins condylomas may be found.



A



B



C

FIG. 571.—TYPICAL LESIONS OF ENDOTHELIOMA (ANGIOSARCOMA).

Note the "punched-out" ulcers in B. C, Endothelioma—tumor cells forming trabeculae; vacuoles in the cytoplasm of individual cells; the coalescence of these vacuoles forms large spaces. × 160. (Case published by *Dr G. J.* [illegible].)



FIG 572.—TYPICAL LESIONS OF SO-CALLED "GRANULOMA ANNULARE" ON THE HANDS.

The arcs and rings are infiltrated and have a granulomatous feel. Lesions may occur on face and neck, and occasionally scattered all over the body. They do not respond to treatment for syphilis. The histology is very characteristic (central caseation with radiating connective tissue strands) and fairly eliminates syphilis in case of doubt.

CHAPTER XVI

LATE SYPHILIS OF THE SKELETAL SYSTEM

The manifestations of early syphilis in skeletal structures have been touched upon in Chapter XII The present chapter deals mainly with the description and diagnosis of the later types of lesions. The rich lymphatic supply of the bone marrow and periosteum the dependent position of the long bones, the slow circulation, all tend to make the osseous structures par ticularly reservoirs for the infection, and to place bone manifestations among the most ubiquitous in the entire symptomatology of the disease.

Syphilis of bony structure occupies, moreover in the general pathology and immunology of syphilis place not unlike that of the skin in that the reaction in these tissues appears to be an important part of the general defence mechanism. DesBrisay and Stokes in study of 206 patients with untreated syphilis, largely of lat type found that syphilis of the nervous system was rare in those who had developed syphilis of the bones. Brunsting and Stokes found the highest proportion of osseous syphilis in Wassermann-fast patients to be associated with syphilis of the skin and the lowest with syphilis of the nervous system. In the Mayo Clinic series it appears that exclusive of tabetic arthropathies, only 24.3 per cent of 70 patients had abnormal spinal fluids, in contrast with 40 per cent in patients with cardiovascular syphilis. As result of the studies of Shaw (1940) and of Wassermann and Goodman (1934) there can be little doubt that neurosyphilis occurs less frequently as an accompaniment of cutaneous and osseous syphilis than it does with other forms of late visceral syphilis. Since neurosyphilis is established early in the course of the disease and late cutaneous and osseous syphilis are not manifest for some years, there is no logical reason to believe that visible lesions of skin, mucous membrane, or bone, protect the central nervous system. Instead, it is to be assumed that the absence of neurosyphilis and the presence of benign late syphilis result from some common factor which is inherent in the infecting organism of the host or which is established early in the course of the disease.

Spirochaeta pallida is, according to Neisser found in the bone marrow within few hours after it has gained entrance to the body The organism has been demonstrated in the bone lesions by Levaditi and Sauvage in 1905 and by many pathologists since then. Chesney has obtained *Spirochaeta pallida* from the synovial fluid of patient with syphilitic arthritis. There is, therefore, no apparent occasion to draw on the conception of syphilotoxin as necessary part of the mechanism of syphilitic joint manifestations.

Frequency of Skeletal Syphilis.—The available literature gives very few suggestions as to the actual frequency of skeletal syphilis. This arises in part from the undoubted existence of unsuspected and symptomless bone lesions demonstrable only by roentgen ray studies on the one hand and, in part, from a tendency on the other hand, to ascribe all bone and joint manifestations occurring in a syphilitic to syphilis. A striking demonstration of the diagnostic *importance of occult bone lesions has taken place in recent years through the* intensive roentgenological studies of the bones in infant prenatal syphilis. So far as we know no routine survey of the entire osseous system in a large number of adult syphilitic patients by all available means has thus far been published. Clinical experience, however suggests that few syphilitic patients indeed manage to escape some degree of reaction in this group of structures at some time in the course of their infection. The proportion of clinically detectable syphilis of the bones will of course vary with the stage of the disease and the thoroughness of the examination. Roentgenology will loom larger in the later than in the earlier years and from the clinical side the late manifestations, relatively

more solitary and more destructive, will seem to bulk larger in the general medical conception of the situation than will the symptomatically important but structurally inconspicuous earlier largely periosteal changes.

Available reports in the literature vary widely as to the frequency of osseous and articular lesions and there is some indication from the more recent studies that they may be becoming much less common manifestations of the disease, as might be expected with the increasingly more satisfactory application of treatment to early syphilis. Wile and Senear in survey of 163 syphilitic patients which was considered representative more than decade ago, found that 60 per cent had osseous or articular lesions. McKelvey and Turner (1934), of 10,000 cases of syphilis in Baltimore found chronic articular lesions of late syphilis in only 0.6 per cent and osseous lesions in 6.8 per cent. Speed and Boyd (1936) state that bone syphilis forms only 0.5 per cent of all admissions to the Campbell Orthopedic Clinic. Buchman and Lieberman (1941) reveal that only 5 per cent of the 2,400 syphilitic patients from among the 185,000 cases admitted in the ten years prior to 1939 to the Hospital for Joint Diseases in New York City had skeletal syphilis. Even then, they felt that the method of selecting the cases would make the proportion abnormally high and not representative of the true *prevalence of this condition.* Kuhns and Polderman (1940) (Boston) while remarking upon the excessive rarity of chronic syphilitic arthritis, state, "we

Fig. #73.

THE PATHOLOGY AND SYMPTOMATOLOGY OF BONE SYPHILIS

PATHOLOGY AND x RAY CHANGES	CLINICAL SYMPTOMATOLOGY
Early Cranial Osteoperiostitis	
This is hypothetically the pathologic equivalent of the symptoms, though not recognizable in life. x-Ray negative.	Cephalgia, intermittent, often nocturnal, sharply regional, often confined to single definitely localized point. Most common in early syphilis.
Acute Early Osteitis	
No demonstrable lesion in life.	Ostealgia or osteocopic pain. Boring in character often but not necessarily nocturnal, aggravated by heat, often relieved by movement, coming on when patient is warm in bed, often at or between certain definite hours.
Early Periostitis	
Thickening and infiltration of the periosteum, edema, chronic low-grade inflammatory changes. Tendency to involve the long bones, most frequently the tibia. Ray negative.	Doughy, non-inflammatory swelling, visible where superposed tissues are thin, as over the tibia. Elsewhere may be palpable as diffuse or fusiform enlargement or merely as tenderness. No hard points.
Late Periostitis	
Tendency to involve long bones and shoulder girdle. Thickening nd infiltration of periosteum, with formation of subperiosteal bone t points where process is chronic, p-pearing as serrations and irregularities. Ray picture of periosteal thickening and elevation, forming irregularities in the outer surface of the shaft without obliteration of the cavity If much subperiosteal bone is formed there is line of increased density along the surface of the bone beneath the periosteum.	Doughy swelling if bone is near the surface, slight general enlargement if deep. Firmer and more nodular than early periostitis, due t deposition of bone. There may be palpable serrations and exostoses. Skin may become livid and fixed at points here it is closely stretched over the bone. Tender point much less sharply marked and less exquisitely sensitive than in early periostitis. Pain may be diffuse or osteocopic in character The process is afebrile

Fig. 273 (*Continued*)

THE PATHOLOGY AND SYMPTOMATOLOGY OF BONE SYPHILIS

PATHOLOGY AND X-RAY CHANGES	CLINICAL SYMPTOMATOLOGY
Osteitis and Osteoperiostitis	
Localizations as in periostitis, but, in addition, involves the bones of the skull and face. Thickening and increased density, usually not uniform, but spotty roughened, and irregular Sequestrum formation in long bones is unusual. Destruction of bone evidenced by pitting of surface. Invasion of the cavities of long bones, with marked thickening of the shaft, but smooth inner surface. In the membrane bones of the face and skull, sequestra are common, with necroses, unaccompanied by productive or regenerative changes. x-Ray picture may range from simple thickening of the shaft of long bone and obliteration of the cavity to extensive combinations of proliferative and destructive lesions, forming exostoses and eburnations with areas of increased density and of rarefaction, and with varying degrees of gummatous destruction and occasional sequestrum formation. In the cranial bones, worm-eaten areas of destruction or sharply defined necroses with no evidence of regenerative or productive processes will be found.	Swelling as in late periostitis, with diffuse tenderness, often not very marked, but with osteocopic pain, sometimes but not necessarily nocturnal. Skin usually not involved until late or gummatous changes occur especially over skull, long bones, and clavicle. When skin breaks down, may form sharply circumscribed ulcer or a sinus with fixation. Sequestrum present in osteitis of the skull and membrane bones of the face and nasal cavity Marked fetor when secondary infection occurs. No fever except in rare cases of marked secondary infection. Sinus formation rare, but possible.
Gummatous Osteomyelitis	
Extensive involvement of the entire bone-marrow with combined proliferative and destructive changes, more marked in general in the less dense bony tissues at the ends of the bones (Dunlop) The secondary involvement of the bone may give rise t rarefactions or thickenings, exostoses, and sieve formations from gummatous destruction along the Haversian canals. Periosteal thickening may be secondary Involvement of the tissues around the affected bone, ith gummatous subcutaneous and cutaneous changes and characteristic lesions may occur. Ray shows the above changes. In the tissues about the involved bones no bone deposits are seen as in the case of sarcoma. Sequestrum may form, but is unusual.	Indolent swelling with pain, but comparatively little constitutional reaction considering the extent of the lesion. Pronounced constitutional reactions are usually associated with secondary infection. Tenderness on pressure rarely marked. No suppuration as rule. If such occurs, it is usually secondary to the formation of cutaneous lesion with gummatous breakdown. N associated glandular involvement. Cutaneous lesions if present may give clue to the identity of the process. Sinus formation possible, but unusual.

were unable to establish diagnosis of syphilitic arthritis in any of our patients. New and Brittingham (1938) report that of 8000 patients consecutively admitted to the syphilis division of the Out-Patient Department of the University of Georgia 61 (0.71 per cent) presented the clinical picture of arthritis.

Importance of Prenatal Infection in the Background of Skeletal Syphilis.—There is probably no single phase of syphilis in which the student of bone

Fig. 874.

THE PATHOLOGY AND SYMPTOMATOLOGY OF JOINT SYPHILIS

PATHOLOGY AND x RAY CHANGES	CLINICAL SYMPTOMATOLOGY
Arthralgia	
No demonstrable changes in the joints. x Ray negative.	An accompaniment of early syphilis. Pain without loss of mobility Worse when quiet, relieved by motion. May be and often is nocturnal. No heat or swelling tenderness, limitation, or crepitation. Slight fever only as an accompaniment of the syphilitic infection.
Hydrarthrosis	
Simple effusion without inflammatory changes in the joint or periarticular tissues. x Ray negative except for enlargement of the joint cavity in marked examples. Little or no impairment of function, though if prolonged may be more marked.	An accompaniment of early and recurrent syphilis and of heredosyphilis. May be sudden of onset, intermittent, and of long duration. Usually bilaterally symmetric and involving knees, elbows, and ankles in order of frequency Peri-articular signs nil no redness, heat, infiltration. Patient afebrile little or no constitutional reaction.
Arthritis, Polyarthritis, and Synovitis (Syphilitic Pseudo-rheumatism)	
Inflammatory changes in the joint with much less destruction than in the infectious arthritides. -Ray often negative, or showing only mild destructive changes.	An unusual accompaniment of early syphilis, though perhaps more common than reported. Tendency t involvement symmetrically of the larger joints, ith little tendency to shift from joint to joint. Less impairment of mobility than would be expected from the degree of involvement. Joint indolent and non-inflammatory compared with the usual acute arthritis. Pain disproportionately small for extent of process. Fever and constitutional disturbance slight considering degree of joint involvement, as compared ith acut infectious arthritis.
Gummatous Osteo-arthritis and Osteochondrodystrophies (Pseudo White Swelling)	
Usually results from extension of gummatous osteomyelitis of the shaft into the joint cavity and almost never occurs as a separat lesion. The destruction of the joint surface is usually at the end of the involved bone and rarely extends to the opposit surface of the joint cavity I extreme cases granulomatous involvement of the periarticular tissues and skin may occur Less destruction than in the corresponding type of tuberculous joint.	Involves large isolated joints, especially knees and elbows, often asymmetric. Enlargement of the joint, pale tense shiny skin. Surprisingly little impairment of mobility for the apparent extent of the process. Ankylosis rare unless secondary infection occurs. Breakdown and suppuration rare but may occur with sinus formation and extension of the process t the skin ith the configuration of lat syphilids. Pain absent or slight. Little constitutional reaction unless due to secondary infection.

lesions should be better versed from the clinical side than in the diagnostic earmarks of prenatal syphilitic infection (Chapter XXI) Particularly in childhood and in the differentiation of tuberculosis, osteomyelitis and sarcoma from syphilis, unfamiliarity with the clinical field and stigmas of prenatal infection has led to almost innumerable and too often serious mistakes. The perfection of roentgenological diagnosis (see p 774) and the increasing tendency to apply serological tests routinely to the study of all bone lesions is fortunately reducing the seriousness of this factor of error in diagnosis. The two types of processes, acquired and prenatal, resemble each other closely osteochondritis and epiphysitis in infancy being the chief distinctive lesions of the prenatal type.

THE PATHOLOGY AND SYMPTOMATOLOGY OF BONE SYPHILIS

The parallel column summary must be invoked here for condensation purposes and the pathology and symptomatology of bone syphilis are therefore reviewed in this fashion in Fig. 573 and of joint syphilis in Fig 574.

Atypical and Rare Conditions.—Articular and periarticular conditions furnish the chief variants on the typical pictures described. The acute syphilitic arthritides may be extremely confusing Chesney Kemp, and Resnik have reported two cases of pseudo-infectious arthritis with fever marked general lymphadenopathy and eosinophilia in which *Spirochaeta pallida* was demonstrated by inoculation in the joint fluids in one of the cases and from an inguinal lymph node draining the knee joint in the other case.

Syphilitic bursitis, described by Verneuil and studied by Churchman, who collected 27 cases, and more recently by Lane, and Garner and Schoch is a gummatous infiltration, usually symmetric, of the bursae over the patellae



Fig. 572 —Macroglossia, with woody infiltration of the base of the tongue and diffuse involvement of buttocks, thighs and calves in patient with an old syphilis. Slight improvement with treatment.

and the olecranon processes. The infiltration may break down or become hard and fibrotic Other bursae when involved present no distinctive signs, the syphilitic factor being discovered by collateral evidence, if at all.

The myopathies of syphilis consist of the myalgias of the secondary period already mentioned and of late gummatous infiltrations, quite rare which may

leave deep deforming scars. Benign infiltrations of the biceps may cause contracture which involutes spontaneously or on treatment.

A diffuse syphilitic myositis is also recognized affecting many of the muscles of the body producing woody infiltration with fibrosis which in its late stages when it is usually recognized is beyond improvement by treatment, although the patients experience some gain in well-being. This type may be relatively nonnflammatory and may even involve the musculature of the tongue as in Fig. 575 In this patient, who had an old syphilitic infection recognized at age sixty-eight, the buttocks, thighs and calves were of wooden hardness, though not resistant to the needle. The condition of the tongue was mistaken for Hodgkin infiltration. Although the serological tests were positive, no biopsy was obtainable, so that the condition could not be differentiated with certainty from diffuse amyloidosis as discussed by Gerstl although there was definite though not marked improvement under treatment with bismuth.

Nodosities occurring about the joints and in the tendon sheaths have aroused much interest, to judge from the recent literature.

According to Jeanner Lutz recognized the condition in the Hawaiian Islands in 1891 and the first complete description of juxta-articular nodules was published by Jeanselme in 1904. Under this designation and that of fibroid gummas of the extremities, a considerable literature collected by Jessner with American examples reported by Goodman and Young, Kalz, Fox, and Brunsting, has accumulated. The condition is rare, perhaps because seldom diagnosed.

The essential lesion is a hard fibrous nodule occurring in some cases along the course of tendon sheaths, particularly on the fingers, and in others as subcutaneous fibrous nodes, often of considerable size, on the extensor aspects of joints, such as the elbows. The lesions must be distinguished from multiple ganglia, simple fibromas, rheumatic and gouty nodules, and xanthomas. The response to treatment for syphilis is usually satisfactory but in one case which we observed, a multiple spondylitis and arthritis in a patient with a positive Wassermann reaction accompanying the condition had apparently not responded as satisfactorily to treatment as did the nodules themselves. The histologic picture is not necessarily characteristic for syphilis.

THE CLINICAL PICTURE OF LATE OSSEOUS AND JOINT SYPHILIS

The analysis of the original Mayo Clinic Group of 239 cases, the essential features of which are summarized in Fig 576 does not differ materially from the 1929–1938 series of Buchman and Lieberman (1941) based upon a somewhat smaller number though more recently studied cases

The Buchman and Lieberman series shows preponderance of males 61 per cent as compared with the Mayo Clinic series 57 per cent a ratio of joint to bone involvement of 1:4, 86 per cent of their congenital syphilis cases and 14 per cent of their acquired bone and joint syphilis had synovitis; previous history of syphilis was obtained in 45 per cent and positive Wassermann in 91 per cent (excluding the Charcot joint cases where the Wassermann was negative in 68 per cent, cf Fig 577) Speed and Boyd (1936) report 90 per cent positive bloods in untreated acquired bone syphilis and also obtained history of definite trauma in 30 per cent.

As result of the review of the older and the current literature, Buchman and Lieberman conclude, "The high incidence of lesions of the bones and joints due to acquired syphilis noted in the literature refers to the older age groups, in which Charcot joints are the predominant lesions; to years past when the diagnostic acumen with reference to lesions of the bones and joint was not as sharp as it is at present, and to the days when any unknown lesion of bone or joint was attributed to syphilis.

If we set aside for the moment consideration of the Charcot joint which forms at the present time the preponderant recognized lesions of skeletal

syphilis (38 per cent in the Buchman and Lieberman series) periostitis is the most frequent bone lesion of late as of early syphilis. Involvement of the periosteum occurred in 53 per cent of the Mayo Clinic series and in 45 per cent of Buchman and Lieberman's series.

Sante points out that *only the lacework or filiform type of periostitis as it* appears in the roentgenogram is characteristic of syphilis, the parallel veiling occurring with trauma and pyogenic infections. Clinically late periostitis dif-

Fig. 270.

LATE BONE AND JOINT SYPHILIS
A Survey of 239 Mayo Clinic Cases

1. Males 57 per cent; females 43 per cent. The latter is one of the highest proportions of women in any late manifestation of the disease.
2. Manual labor more frequent than sedentary type (traumatic factor?)
3. Cranial bone (12 per cent) and tibial lesions (20 per cent) head the list.
4. Shoulder girdle lesions (including sternum and ribs) rank next (10 per cent) and are most destructive (clavicle 7.5 per cent).
5. Spondylitis 6 per cent femur 4.5 per cent; humerus 3.5 per cent, fibula 4 per cent forearm and hand 2.5 per cent.
6. Ratio of joint to bone involvement 1 7 (20 to 130). Wile and Senear 1 3 (21 to 60)
7. On relative frequency of involvement of joints, no agreement on details in the literature but knee always leads, ankle or wrist next (Clark found hip and shoulder at autopsy 26 cases), spine and fingers last.
8. Periostitis is overwhelmingly th commonest lesion (53 per cent)
9. Osteomyelitis (20 per cent); arthritis 12 per cent; osteitis, spondylitis 6 per cent each; synovitis 2 per cent (chronic) Acute synovitis, not one case in 12,000 syphilitic patients (rare).
10. Pain and swelling the chief symptoms (71 per cent, 21 per cent). Tumor 10 per cent; ulceration 9 per cent; "rheumatism 8 per cent.
11. Nocturnal pain (overemphasized in literature?) 14 per cent.
12. Traumatic factor (overemphasized in literature?) 25 per cent only
13. Wassermann positiv after entry 88 per cent. (Would probably be higher by more sensitive tests.)
14. Wassermann had been taken before entry in only 24 per cent.
15. Syphilis diagnosed before entry 7 per cent. History positive (chancre) 26 per cent. Gonorrhea only 25 7 per cent.
16. Roentgen-ray made the diagnosis outright in 48.3 per cent; was negative in 28 per cent.
17. Characteristic syphilids of skin present on entry 18 per cent; active 43 per cent; scars 4 per cent; genital scars 11 per cent.
18. Liver enlarged 11 per cent.
19. Abnormal spinal fluids 24.5 per cent.

Pain and swelling in characteristic location, with disability slight and little constitutional reaction in proportion to the marked roentgen-ray changes; an bsence of suppuration and no local glandular enlargement, arouse strong suspicion of syphilis.

fers from early periostitis in a greater tendency to production of bone which is responsible for the visible roentgenological findings, and yields on examination a distinct thickening and irregularity of the bone surface, often in the older parts of the process not even tender to pressure. It is this diffuse proliferative process *which produces the marked palpable, sometimes almost* fusiform thickening of the tibia and in the shoulder girdle, the thickened inner third of the clavicle which is often so effective as a suspicion-arouser The tibia and the shoulder girdle stand out as the two bony structures detailed exami-

nation of which should never be overlooked in a general examination where syphilis is to be detected

Next after the periosteal lesion comes osteomyelitis. Sante points out that the roentgenological appearances of syphilitic osteomyelitis are distinguished with difficulty from those of the pyogenic process, the difference being based in diagnosis upon the comparative mildness of the clinical manifestations in syphilitic osteomyelitis

Syphilitic osteitis, the least common of the bone lesions of late syphilis, assumes either a diffuse or a localized gummatous form. In the former a dense thickened irregularity of the cortex develops, seldom attended, according to Sante by periosteal reactions. In the localized gummatous process, an area of cortical necrosis and destruction appears, a sequestrum being formed and the periphery of the process presenting a scalloped circinate border about which a dense sclerosis of bone develops.

Syphilitic joint lesions with the exception of Charcot joint apparently tend to become less frequent later in the disease. They constitute only 12 per cent of the lesions, in our experience. As in the case of bone lesions, the traumatic factor appears to be of less importance than the older literature tends to indicate There are none the less, unescapable instances of the relationship, as in the case recently described by Lanyar Steinbrinck has well summarized the special diagnostic features of joint syphilis (1) the localization, on which, however there is widespread disagreement as to frequency (2) The contours of the joints are lost, sometimes with sometimes without the presence of fluid, and sometimes through marked thickening of the capsule (3) The indolence of the joint is striking and comparative freedom of movement should always arouse suspicion of syphilis. Steinbrinck emphasizes in joint syphilis the importance of nocturnal pain and periods of complete remission, which cannot be regarded as entirely trustworthy in the pain of bone syphilis as such. The pain is described as boring tearing throbbing, or cutting and disappears usually toward morning and is not invariably confined to the joint. Schlesinger (cited by Steinbrinck) emphasizes the characteristic tender points, particularly at the condyle and epicondyle of the knee, more frequently found in syphilitic than in other joint involvement. Good functional use of a joint is more characteristic of active syphilis than any other arthritic lesion, and fluid is, on the whole, absent rather than present.

Great importance is attached to the resistance offered by syphilitic arthritides even to intensive treatment for articular rheumatism. This refractoriness involves the fever and constitutional symptoms quite as much as the local joint manifestations.

In the performance of therapeutic tests, special importance attaches to the Herxheimer flare-up which however may be entirely absent, the pain often disappearing at once in the earlier types of lesion The constitutional concomitance of fever and systemic reaction should be watched for Relapse follows promptly upon a premature suspension of treatment.

The Charcot Joint.—Evidence has been accumulating in recent years to indicate that this type of joint lesion formerly accepted as an exclusive concomitant of tabes dorsalis is in reality a neuro-arthropathy with several possible causes. The clinical characteristics of this type of joint which should not properly be described as an example of syphilis of the articular structures as such, is summarized from a combination of the literature and especially Wile and Butler's observations on 88 cases and Stokes's on 30 cases in Fig 577

Steindler in an excellent review of the tabetic arthropathies emphasizes the importance of spontaneous fracture as an early warning of tabes. He urges early recognition with protection, stabilization and alignment of the Charcot joint. The general diagnostician and the orthopedist should be cautious, we believe in making diagnoses of "*burnt-out tabes*" in patients with negative

Fig. 577

THE CHARCOT JOINT

1. Described by Charcot in 1868.
2. An associated manifestation of tabes dorsalis, though not invariably so (Wile Butler Stokes) (Syringomyelia, spina bifida, cord injury leprosy (Soto-Hall and Haldeman) idiopathic. For bibliography see Wile and Butler)
3. Two types, hypertrophic, atrophic.
4. Clinical characteristics
   (a) Sixty to 90 per cent males.
   (b) Onset gradual.
   ( ) Knee 60 per cent, ankle 25 per cent (Wile and Butler). Our experience puts foot and ankle first. Any *joint* may be involved.
   (d) Hydrops at onset 63 per cent—usually the first symptom.
   (e) Pain at onset 30 per cent. Often relieved by treatment for syphilis.
   (f) Loss of contours, hypermobility painlessness, "bag of bones feel mark the fully developed joint.
   (g) Multiple joint involvement not common (23 per cent)
5. Roentgenological diagnosis—78–100 per cent. Often worth while to examine apparently uninvolved joints (Dunlop, Wile and Butler)
6. Roentgenographic characteristics in the early stages shows only collection of fluid within the synovial sac, which is difficult to recognize except after considerable study especially in the smaller joints. As the process progresses there is a thinning of the articular cartilages, with sclerosis of the subchondral bone which is so slight at first that it is easily overlooked by the inexperienced. When marginal fractures occur the process of osteosclerosis just mentioned will be marked in some areas alternating with atrophy in others. From this point the process progresses to complet disorganization of the joint with loose bodies in the joint cavity and the formation of new (parosteal) bone outside the joint cavity
7. Trauma a predisposing cause in only 17 to 24 per cent. More often occurs as consequence in previously diseased joint.
8. Recent views of etiology include Eloesser Wile and Butler (trauma and loss of protective pain sense), Philips Rosenbeck (peripheral nerve degeneration).
9. Blood Wassermann reaction negative in 44–76 per cent.
10. Spinal fluid negative in 50 per cent.
11. Indubitable tabes or taboparesis in 81 to 97 per cent (Wile and Butler)
12. Asymptomatic neurosyphilis, spinal fluid positive in 12 per cent (Wile and Butler)
13. All other causes and associations 3 per cent.
14. Commonest diagnostic errors (20 per cent of cases) arthritis, tuberculosis (including Pott disease), dislocation.
15. While usually inactive or only slightly active, the tabes is not always "burnt out.
16. For treatment see p. 790.

EXAMINE THE PUPILS IN EVERY CASE OF SWOLLEN JOINT

blood serologic reactions and negative spinal fluids associated with joint conditions, and in particular with Charcot joints. A rather large proportion of our cases of Charcot joint present this peculiarity and exhibit in the course of years of observation definite evidence that the tabes is progressive. Treatment for tabes should not, therefore, be withheld merely because of negative serologic findings (see Management of the Charcot Joint, p. 790)

O'Leary (1936) as spokesman for the coöperative clinic group found that the prevalence of Charcot joint as a symptom of tabes dorsalis was 48 in 775 males (6.2 per cent) and 16 in 210 women (7.6 per cent). One fifth had completely negative blood and spinal fluid when Charcot joint first appeared, one fifth had Group III spinal fluid, 55 per cent Group II and 5 per cent Group I. As Soto-Hall and Haldeman (1940) have pointed out, therefore, the preponderance of Charcot joint among males does not result from increased susceptibility to joint involvement as such but to the underlying predisposing cause (tabes dorsalis) which is much more frequent in men than in women. For similar reasons tabetic arthropathy is uncommon among the colored as compared to white, even though bone and joint syphilis as such is approximately five times more frequent among the colored. (Pomerantz and Rothberg (1941)) The average age of onset of Charcot joint is between forty and fifty years, though cases are reported from congenital syphilis in the second decade and some cases have their onset infrequently as late as the seventh decade.

THE DIAGNOSIS OF SYPHILIS OF THE SKELETAL SYSTEM

Tradition and therapeutic exigency have made bone lesions primarily surgical matters, and as such a somewhat too ready appeal is often made to therapeutic instead of diagnostic procedure. The first impulse seems to be to aspirate, to open up, to drain, to immobilize, to embed in plaster, to put on a brace, instead of to take a careful history, to make a complete physical examination, to study the pupils and reflexes, to perform serological tests on the blood, and microscopic and inoculation studies of exudates and so forth. *The first approach to bone lesions must be medical and diagnostic,* rather than surgical and therapeutic, if serious blunders with respect to syphilis are to be avoided. Our personal experience with diagnosis in this field has indicated a rather low index of suspicion with reference to syphilis, as the case histories will show.

Syphilitic lesions of the bone are less specific in their characteristics than are those of the skin. Clear-cut though verbal description may appear to be, particularly when based on the developments of roentgenology, yet so far as specificity is concerned, much still remains to be desired. Speaking from the experience of the Mayo Clinic series, the outright diagnosis of syphilis of the osseous system cannot be made by any one method in a higher proportion than 50 per cent. We have repeatedly been told by roentgenologists that the only genuinely specific picture in roentgenological syphilology is that of the Charcot joint. In infancy, the parallel or line type of periostitis of the long bones is often accepted as almost pathognomonic of syphilis, but the fact remains that the lower specificity of the clinical picture in syphilis of the bones compels constant and close attention to collateral evidence, and the *utilization of all possible aids to a diagnosis of syphilis. It is therefore particularly worth while to analyze in a little greater detail the items of procedure which* are of the greatest service in its recognition.

The Routine Blood Serological Test the First Essential.—When called upon in routine teaching to offer the nearest approach to a touchstone in this field, experience compels us to place the absolutely routine performance of blood serological tests on all patients with bone and joint lesions without exception, as the most valuable guide to a syphilitic factor in the situation. With the inclusion of the Charcot arthropathy, the emphasis shifts somewhat toward the systematic and complete physical examination with a special reference *to pupillary reflexes, deep reflexes, station* and so forth in older patients, for in the Charcot joint of all others the serological test may fail.

The Roentgenographic Factor in Diagnosis.—Next to the routine use of serological tests should be placed the skilled interpretation of the roentgeno-

gram. In the Mayo Clinic series, abnormalities appeared in 72 per cent of the cases, the symptom-producing structure being negative to roentgenogram in 28 per cent. This figure will of course vary upward and downward with the type of material, being lower in a material rich in early syphilis and higher where the proportion of prenatal syphilitic cases is large. While abnormalities appeared in 72 per cent, in only 48 per cent was a diagnosis made outright, the opinion being couched in merely descriptive terms in 21 per cent of cases but being erroneous in only 1 case a truly enviable diagnostic record

It is impossible here to go in detail into the roentgenographic differentiation of syphilis, osteomyelitis, sarcoma and tuberculosis by the roentgen-ray as was done in the case of the skin for the method is essentially too special to be available to the average physician. He must take the assurance of a competent roentgenologist as to whether or not the plates from a clinically observed lesion suggest syphilis or not. It is none the less useful for the diagnostician to have some conception of the appearance of a bone or joint lesion in the roentgenogram as a guide to the inspection of such plates as he may have the opportunity to see in conjunction with his clinical work. The following brief description collected from the literature is, therefore, offered in addition to the descriptive comments already made.

Syphilis Preponderantly Constructive, Osteoplastic Process.—The best account of the changes induced by syphilis in the bones and joints as seen by radiologist, with which we are familiar is that of Skinner He points out that the radiographic findings are explained by the fundamental pathology of the disease. Syphilis is usually constructive, osteoplastic process. Even in the osteoporotic changes of the cranial bones he believes that there is an early osteoplastic phase followed by later destructive changes. Bone lesions in general are divisible into two types, preponderantly constructive, as in osteomyelitis and syphilis, and preponderantly destructive as in tuberculosis and malignancy Constructive or bone-producing lesions are therefore open to the suspicion of being syphilitic or osteomyelitic in origin. The chief exception to the constructive or productive rule in syphilis is in the case of the cranial bones, in which the ultimate destructive process, without reconstruction, leaves the diagnosis suspended between syphilis and malignancy Since primary malignancy of the cranial bones is uncommon, it follows that destructive process in the cranial bones is, in the absence of primary malignant focus elsewhere, almost surely of syphilitic origin, especially in patient of precancerous age.

Differentiation of Specific from Nonspecific Periosteal Lesions.—In syphilis of the long bones, Blaine, Diefenbach, and Brickner (quoted by Carman) point out that syphilitic periostitis is sometimes distinguished with difficulty from nonspecific inflammatory changes in the periosteum. Essential points in the differentiation include

1. Irregular contour of the periosteum.

2. Moth-eaten or reticulated appearance of the tissue hen the contour of the periosteum is destroyed.

3. Sclerosis or increased density of bone shadow constant accompaniment of syphilitic invasion.

4 Bulging of the periosteum along such surfaces as the anterior aspect of the tibia. Brickner states that syphilitic periostitis begins next to the bone as subperiosteal infiltration, so that the periosteal shadow which in the early stages is usually narrow is lifted way from the bone. In advanced conditions, as in localized periostitis gummosa, the shadow acquires considerable density hile palpable periosteal gumma, being merely inflammatory causes no shadow Skinner calls attention to the parallel veiling of the shaft between the osteogenetic zone of the periosteum and the normal bone cortex, hich he interprets as diagnostic of syphilitic periostitis. So long as no gummatous degenerative changes occur this veiling is maintained, but once the process invades the cortex proper there is an immediate reaction with the formation of new deposits which, as throughout the entire picture of bone syphilis and osteomyelitis, exhibit the richness in lime salts hich leads to the production of sharp contrasting shadows to represent the new formation, side by side with the thinning and decalcification hich represent the destructive phase. Bone destruction due to gumma, as Brickner points out, produces light areas surrounded by dark shadow of reactive bone formation or thickening, which distinguishes this condition from osseous tumors and tuberculosis. When gumma surrounds an island of bone

it appears in the roentgenogram as sequestrum, which, however is unusual in unmixed syphilitic osteomyelitis, and forms a contrasting point with tuberculous and pyogenic osteomyelitis. Hodges, Phemister and Brunschwig (1941) point out that the presence of a large sequestrum is strong evidence of pyogenic osteomyelitis and against syphilis. If sequestra from syphilis are demonstrable, *they are usually located in the cancellous regions. The only exception to this is the vault* of the skull where large masses of bone may be sequestrated. Erdheim (1932) remarks that in syphilis of the skull, the outer table is usually much more extensively involved than the inner table valuable point of distinction from tuberculosis of the skull in which the reverse is usually true.

Syphilitic Dactylitis.—In syphilitic dactylitis, as distinguished from tuberculous dactylitis, the shaft usually escapes involvement in syphilis, but is invaded by the destructive process in tuberculosis. In tuberculosis the periosteum bulges in sharply defined area about a destructive lesion in the shaft. In syphilis, on the other hand, the veiling runs parallel to the cortex, and the shaft remains relatively clear Skinner believes that the herringbone serration of the cranial bones, with accentuation of the diploic channels and thickening of the skull, with ill-defined scalloping of the inner table is suggestive of cerebrospinal syphilis.

Radiographic Changes in Joints.—Syphilitic involvement of the joints early in the disease does not, according to most authors, present a characteristic picture, or one that can be safely distinguished by roentgen-ray alone from acute articular rheumatism Hydrops of the joint, according to Skinner is an important early sign. Ely differentiates synovial form, bony form, multi-articular variety and the Charcot joint. The changes observed are usually markedly *less than the clinical pathology would lead one to expect. The outlines of the articulation* (excluding Charcot joint) tend to remain clear and distinct periosteal thickening is apparent at the line of junction of epiphysis and diaphysis. If the bone proper is involved, the changes follow the rules for bone changes elsewhere. There is characteristic increase in shadow density above the seat of the active osteitis, with thinning in the center of activity Destructive areas, according to Young, are sharply defined and do not have the mottled, spotted, or indistinct and grossly irregular ppearance of malignancy Gummatous changes except gummatous chondritis are easily recognized by the same signs of destruction in the light areas surrounded by denser reactive deposits. The identification of syphilitic change in pseudotuberculous joint in an adult may depend upon the finding of signs of old periostitus, thickening and striation t the junction of epiphysis and diaphysis. Some syphilitic joint pictures may according to Ely be differentiated from tuberculosis, radiographically only with the greatest difficulty if at all, the diagnosis depending on collateral findings. The proliferative tendency of the syphilitic process may make the differentiation from nonspecific inflammatory joint processes other than tuberculous quite difficult.

The radiographic differentiation of syphilis from tuberculosis of osseous structures in general then, as Skinner points out, rests upon the contrast between a productive picture as seen in syphilis and a destructive lesion producing rarefaction and general myelomalacia with a notable absence of proliferative reaction, as seen in tuberculosis. The radiograms of tuberculous processes reveal a thinness and lack of definition which is an important differential aid. Skinner emphasizes, however the importance of avoiding confusion with the atrophic changes of disuse. The roentgenologic picture of Charcot joint is summarized in item 6 Fig 577

Th Osseous Lesions of Prenatal Syphilis from the Roentgenological Standpoint.—Stafford McLean (1931) comprehensive and clinically helpful study of the roentgenographic diagnosis of early congenital syphilis, embracing report of 102 cases with more than 1600 roentgenograms, still remains the most significant contribution in this field. Pehu and Policard have contributed extensively t the French literature Excellent summaries of the literature and of the authors experience with the report of case of cystic bone changes in prenatal syphilis, are those of Pendergrass and Bromer and Pendergrass, Gilman and Castleton. The latter report deals primarily with the changes of late syphilis, while the work of McLean deals with prenatal syphilis in the first year of lif

Th Early Lesions.—Of McLean patients, 72 per cent were in the first three months of life and 90 per cent ere not over six months of age. During the first six months of life the sites of predilection of osseous syphilis are the temporary zones of calcification (metaphyses) and the periosteum. After the age of six months, in the infants who survive, the early bone lesions tend to

regress spontaneously even in the untreated case and roentgenologic evidence tends to become insufficient without collateral help. After the first and up to the fourth year of life, prenatal syphilitic bone lesions are probably largely due to relapse of an incompletely healed lesion of early life. They are generally manifested as subperiosteal overgrowth which cloaks osteomyelitis. The favorite sites are the metacarpal bones and the phalanges, but other long or flat bones may be involved. I 53.3 per cent of McLean series in which the clinical manifestations were rated as severe, and *in an additional 27 per cent, the diagnosis* could have been made by scrupulous clinician in nearly every instance, but in third group of masked symptoms, constituting 16.4 per cent, the combined aid of the roentgen rays and laboratory data was required.

Inability or definite disinclination to move one or two extremities, constituting or simulating the Parrot pseudoparalysis, appeared in 32.3 per cent of the children, but could not be interpreted as definite evidence of epiphyseal separation, which occurred in only 23.5 per cent of cases. The blood serological test was positive in 85 out of 96 patients. Spirochetes were obtained by the darkfield method in less than 10 per cent of the cases from the skin lesions. The mortality in the group was high, attesting the severity of the process, 42.1 per cent dying, including 46 5 per cent of those in the first three months of life. Prematurity seems to be marked by definite tendency in the first two months of li t present deep zones of submetaphyseal rarefaction. There is also an absence of marked subperiosteal thickening of the bones in these cases. Severe anemia in prenatal syphilis as found to be associated with severe osseous lesions.

Osteochondritis appeared in 90 per cent of the cases; periostitis in the form of exaggerated subperiosteal bone production, in 70 per cent, osteomyelitis in 46 per cent, and osteitis in 7 per cent. Periostitis was the only discoverable roentgen lesion in only 5 per cent. A combination of rickets and syphilis occurred in 8 per cent. The tibia was demonstrably involved in 87 per cent, the ulna in almost exactly the same proportion the radius in 91 per cent; the femur in 79 per cent; the humerus in 74 per cent, the fibula in 78 per cent. The distal ends of the radius and ulna are the metaphyses most frequently involved.

McLean gives as practically pathognomonic of prenatal syphilis the following types of roentgen lesions hen recognized in the first months of life.

1 Well-defined saw-tooth metaphyses in well-calcified bones.

2. Deep zones (in the longitudinal axis) of submetaphyseal rarefaction.

3. Multiple separation of epiphyses, with or without impaction in bones which are not rachitic.

4 Bilateral symmetrical osteomyelitis of the proximal mesial aspects of the tibiae.

5. Multiple circumscribed osteomyelitis of the long bones. Shown by the roentgen rays as patchy areas of rarefaction.

6. Multiple longitudinal areas of rarefaction (osteomyelitis) in the shafts of the long bones sometimes resulting in fractures.

7 Destructive lesions at the mesial or lateral parts of the metaphyses (foci of rarefaction).

8. Multiple areas of cortical destruction, generally seen within centimeter of the ends of the bones.

9. Double zone of rarefaction at ends of bones.

10. Localized periosteal cloaking occurring in more than one bone.

He states that periostitis (abnormal subperiosteal bone production) does not equal in diagnostic importance the changes at the ends of the bones, since it rarely occurs alone in the first months of life, the age period most important in diagnosis, and in most instances *it initiates* the healing of osteochondritis or osteomyelitis. Periosteal veiling may be of rachitic origin, while in marked syphilitic subperiosteal thickening in the first months of life, metaphyseal lesions always coexist. Subperiosteal multilayered cloaking, the most spectacular roentgen observation, may be present as the predominating lesion after the fourth month and as the sole active lesion after the fifth month of life. At this age and up to the early part of the second year it is of great diagnostic importance.

Lesions of the tarsal, metatarsal, and metacarpal bones and phalanges, in our experience, do not occur in the first months of life except when the larger bones of the extremities are involved. Likewise, lesions of the scapula, clavicle, ribs, ilium, and vertebrae are seen only when the long bones of the extremities are involved. The discovery of such lesions is of greater academic than practical importance

Syphilitic lesions are always distributed bilaterally and in the first months of life lesion of single bone has, in McLean experience, never been due to syphilis.

In his conclusions McLean points out that the roentgenogram may offer means of excluding the diagnosis of prenatal syphilis without apprising the parent of the fact that the infant suspected of having the condition. This is especially true in infants in the first weeks of life with weakness of one or more extremities. In 2 of 102 cases the roentgen rays revealed the diag-

nosis before positive tests of the serums were obtained. Bone lesions roentgenologically recognized may also produce evidence of the severity of the infection in cases with mild cutaneous manifestations. Although the lesions will sometimes involute spontaneously they form valuable guide to the effect of treatment. Roentgenological diagnosis is more valuable than microscopical section.

More recent work has tended to show that many of the bone lesions of early congenital syphilis lack absolute specificity as is the case with similar lesions of acquired syphilis, but these observations have tended to strengthen rather than reduce the value of roentgenographic diagnosis in early infancy as has been shown by Ingraham, Shaffer Spence and Gordon (1941) The work of Ingraham (1936) suggests that the lag phase from infection of the fetus in utero until roentgenographically demonstrable lesions appear approximates five weeks for syphilitic osteochondritis and four months for syphilitic periostitis The presence of irrefutably syphilitic osteochondritis or periostitis in the absence of a positive blood serologic test for syphilis, although it occurs (Ingraham, 1935 McCord, 1936) is an excessively rare clinical finding (Black, 1939). Some of the conditions which must be carefully considered when interpreting the roentgenogram of an infant suspected of having syphilis, shortly after birth are (1) antepartum bismuth therapy in the mother (Caffey 1937 Christie, 1939 Whitridge, 1940) (2) bacteremia, including septicemia, pneumococcemia, gonococcemia and hematogenous tuberculosis (3) malnutrition, including rickets (4) erythroblastosis foetalis (5) trauma, including birth injuries from difficult deliveries (Caffey 1939 Evans, 1940) All of the foregoing may produce changes in the roentgenogram which may under certain circumstances, be confused with syphilis.

The application of these studies to the diagnosis of early congenital syphilis will be discussed in Chapter XXI, Familial and Prenatal Syphilis.

Park and Jackson (1938) have done much to correlate the roentgenographic with the pathologic findings of syphilitic osteochondritis. They have found that a well defined saw tooth appearance in the ends of the long bones is not constant feature of infantile congenital syphilis. It is usually absent hen syphilitic involvement of the bones is slight and may be absent even if the involvement is severe. The most rapidly growing bones are commonly affected and this almost pathognomonic type of syphilitic osteochondritis is found in decreasing order of frequency in (1) Anterior ends of middle ribs (2) lower end of the femur (3) upper end of the femur (4) both ends of the tibia (5) upper end of the humerus and (6) lower ends of the radius and ulna. It is never found in the upper end of the ulna, occasionally only in the upper end of the radius and rarely in the lower end of the humerus. Other factors affecting the demonstrability of these lesions, however make their practical demonstration often easier in the distal metaphyses of the radius and ulna (Ingraham (1935))

Prior to birth the involvement of the ends of the bones is generally proportional to the rat of growth, but after birth the bones are no longer affected so uniformly because trauma and muscle strain alter the vascular supply and with it bone growth and the distribution of *Spirochaeta pallida*.

Th Late Lesions.—Pendergrass, Gilman and Castleton, in discussing the late bone manifestations of prenatal syphilis, found them t occur most frequently between the fifth and the twelfth year and to involve the tibia and elbow especially Multiple bone involvement is often seen with joint changes, usually secondary while in infancy osteoperiostitis, hen it occurs, is found as generalized lesion affecting mainly the ends of the long bones. The tendency in later childhood is involvement principally or solely of the shaft. Here injury plays an increasingly important part in the bone selectivity directly proportional to the age of the child. The onset is gradual and generally accompanied by pain (orse t night) often described by the parent subsequently as rheumatic or growing pains Weber has called ttention to the absence of or but relatively slight pain that is seen in some instances. A symmetrical and tender swelling comes with functional disability proportionat to the pain or to the proximity of the joint. Subsidence of the acut process may be followed by secondary osteomyelitis or gummatous ulceration, but more commonly the typical bone deformities develop, ranging from but slight roentgen changes to the markedly bowed nd thickened saber tibiae. The less common gummata, osteoporosis, and Charcot joint changes are recognized and diagnosed exactly as in the acquired form of the disease. Additional evidence of prenatal syphilis may often be the deciding factor in the early recognition of minor bone changes (i. eyes facies, teeth) and while the complement fixation test is valuable adjunct in children, it tends to be of considerably less value in the older patient.

The bilaterally symmetrical synovitis and periarticular infiltration more or less characteristic of prenatal syphilis were described by Clutton in 1886. The roentgenological findings are not typical but do show some periarticular swelling and possibly some effusion into the joint. The clinical manifestations of Clutton joints are described in the chapter on familial nd prenatal syphilis.

Hypertrophic and atrophic changes, with or without loose bodies diaphysitis, periostitis, and dactylitis occur in late prenatal syphilis, together with condensing osteitis of the skull. The new formation of bone in the syphilitic periostitis is laid down perpendicular to the shaft, or long axis of the bone and therefore requires careful differentiation from the perpendicular striation of osteogenic sarcoma, as Pendergrass, *et al.* point out. In ordinary osteomyelitis the periosteal new bone is laid down parallel to the shaft. In dactylitis or periostitis of the bones of the hands and feet, however the bone is laid down parallel to the shaft.

Diagnosis by Associated Cutaneous Lesions.—From our experience, at least, we may say that it is quite as important for orthopedists and surgeons who deal with the skeletal structures to be competent dermatosyphilologists, as good radiologists. The skin in our group furnished almost as many clues to diagnosis (48 per cent) as did the roentgen-ray and, in many cases, would, if correctly interpreted, have furnished the necessary clue to prevent a diagnostic error The case reports in this chapter contain a number of examples in which the ability of the attending physician to recognize a late syphilis *would have shortened by months or years the course of the osseous lesion. In* occasional instances the cutaneous lesion made the diagnosis over a negative blood serological reaction, especially in the earlier years of the dermatological service, when a less sensitive blood test was in use. Active cutaneous lesions were present in 43 per cent of our cases, scars in 4 per cent, and genital scars in 11 per cent. In dealing with ulcerative lesions of the lower extremities, particularly those over the tibia, a nonspecific usually asymptomatic focal periostitis may apparently develop In attempting to establish the syphilitic character of a suspected cutaneous lesion or *vice versa*, care must be exercised to avoid misinterpretation of traumatic infected and anemic stasis ulcers. The syphilitic nature of either bone or skin lesions is in such cases best determined on the individual merits of the lesion and collateral evidence. Ormsby believes that a leg ulcer which has at one time had syphilitic characteristics may through the course of years, as a result of scarring and vascular changes, assume the appearance of a banal anemic or varicose ulcer Kilbourne believes that therapeutic tests should be performed in doubtful cases with negative serological tests, using bismuth and iodide rather than the arsphenamines.

Diagnostic Value of Clinical Symptomatology—At the close of Fig 576 is an attempt to summarize in a single sentence those features of clinical symptomatology which in the presence perhaps of equivocal findings on examination, may tend to suggest syphilis and the need for a therapeutic test to the critical examiner Pain and swelling, a characteristic location (and search should be made particularly of the tibia and the shoulder-girdle regions) with disability and constitutional reaction slight in proportion to the marked x-ray changes an absence of suppuration and no local glandular enlargement should arouse strong suspicion of syphilis. One or another and combinations of several of these symptomatic criteria, are helpful especially in differentiating gonorrheal and rheumatoid arthritic processes, acute suppurative osteomyelitis (emphasized by Santo) from processes similar in clinical type but in which the etiologic agent is *Spirochaeta pallida.*

Collateral Findings.—In our résumé history of primary lesion appeared in 30 per cent and of gonorrhea only in 23.7 per cent of patients (Fig. 576). Attention might be called to the proportion of enlarged livers in our series in order to add one more to the list of suspicion-arousers in the general medical examination which may start clue leading to the detection of syphilis, if it is present. Enlargement of the spleen occurred in only one case.

Among the negative findings, one of the most interesting is the practically complete absence of cardiovascular lesions among patients with bone and joint involvement. Not more than 6 patients presented any cardiac abnormality whatever This may however be an offshoot of the

nosis before positive tests of the serums were obtained. Bone lesions roentgenologically recognized may also produce evidence of the severity of the infection in cases with mild cutaneous manifestations. Although the lesions will sometimes involute spontaneously they form valuable guide t the effect of treatment. Roentgenological diagnosis is more valuable than microscopical section.

More recent work has tended to show that many of the bone lesions of early congenital syphilis lack absolut specificity as is the case ith similar lesions of acquired syphilis, but these observations have tended to strengthen rather than reduce the value of roentgenographic diagnosis in early infancy as has been shown by Ingraham, Shaffer Spence and Gordon (1941). The work of Ingraham (1936) suggests that the lag phase from infection of the fetus in utero until roentgenographically demonstrable lesions appear approximates five weeks for syphilitic osteochondritis and four months for syphilitic periostitis. The presence of irrefutably syphilitic osteochondritis or periostitis in the absence of positive blood serologic test for syphilis, although it occurs (Ingraham, 1935, McCord, 1933) is an excessively rare clinical finding (Black, 1939). Some of the conditions which must be carefully considered when interpreting the roentgenogram of an infant suspected of having syphilis, shortly after birth are (1) antepartum bismuth therapy in the mother (Caffey 1937 Christie 1939, Whitridge, 1940.) (2) bacteremia, including septicemia, pneumococcemia, gonococcemia and hematogenous tuberculosis (3) malnutrition, including rickets (4) erythroblastosis foetalis (5) trauma, including birth injuries from difficult deliveries (Caffey 1939 Evans, 1940) All of the foregoing may produce changes in the roentgenogram which may under certain circumstances, be confused with syphilis.

The application of these studies to the diagnosis of early congenital syphilis ill be discussed in Chapter XXI, F milial and Prenatal Syphilis.

Park and Jackson (1936) have done much to correlate the roentgenographic ith the pathologic findings of syphilitic osteochondritis. They have found that a well defined sawtooth appearance in the ends of the long bones is not constant feature of infantile congenital syphilis. It is usually absent when syphilitic involvement of the bones is slight and may be absent even if the involvement is severe The most rapidly growing bones are commonly affected and this almost pathognomonic type of syphilitic osteochondritis is found in decreasing order of frequency in (1) Anterior ends of middle ribs (2) lower end of the femur (3) upper end of the femur (4) both ends of the tibia (5) upper end of the humerus and (6) lower ends of the radius and ulna. It is never found in the upper end of the ulna, occasionally only in the upper end of the radius and rarely in the lower end of the humerus. Other factors affecting the demonstrability of these lesions, however make their practical demonstration often easier in the distal metaphyses of the radius nd ulna (Ingraham (1935))

Prior t birth the involvement of the ends of the bones is generally proportional to the rate of growth, but after birth the bones are no longer affected so uniformly because trauma and muscle strain alter the vascular supply and with it bone growth and the distribution of *Spirochaeta pallida*.

The Late Lesions.—Pendergrass, Gilman and Cartleton, in discussing the late bone manifestations of prenatal syphilis, found them t occur most frequently bet een the fifth and the t elfth year and t involve the tibia and elbow especially Multiple bone involvement is often seen with joint hanges, usually secondary while in infancy osteoperiostitis, when it occurs, is found generalized lesion affecting mainly the ends of the long bones. The tendency in later hildhood is involvement principally or solely of the shaft. Here injury plays an increasingly important part in the bone selectivity directly proportional to the age of the child. The onset is gradual and generally accompanied by pai (orse t night) often described by the parent subsequently as rheumatic or growing pains Weber has called attention t the absence of or but relatively slight pain that is seen in some instances. A symmetrical and tender swelling comes with functional disability proportional to the pai or t the proximity of the joint. Subsidence of the acut process may be followed by secondary osteomyelitis or gummatous ulceration, but more commonly the typical bone deformities develop, ranging from but slight roentgen changes to the markedly bowed nd thickened saber tibiae. The less common gummata, osteoporosis, and Charcot joint changes are recognized and diagnosed exactly as in the acquired form of the disease Additional evidence of prenatal syphilis may often be the deciding factor in the early recognition of minor bone changes (eyes, facies, teeth) and hile the complement fixation test is valuable adjunct in children, it tend to be of considerably less value in the older patient.

The bilaterally symmetrical synovitis and periarticular infiltration more or less characteristic of prenatal syphilis were described by Clutton in 1886. The roentgenological findings are not typical but do show some periarticular swelling and possibly some effusion into the joint. The clinical manifestations of Clutton joints are described in the chapter on familial and prenatal syphilis.

the range of manifestations between Fig 607 diagnosed as tuberculous, but actually syphilitic, and Fig. 612, diagnosed as syphilitic on the basis of a response to arsphenamine, but probably tuberculous, seems in the present state of knowledge to be too hazardous for full acceptance. Congenital and child hood syphilitic infections associated with tuberculous adenitis and white swelling of the knee or Pott s disease of the spine, produce pictures in which it is difficult to unravel the respective instrumentalities of the two infections. Alexander and Schoch (1942) have rediscussed this question in the light of their recent case reports.

Confusion of Syphilitic Osteochondritis and Tuberculous White Swelling.—Probably the commonest error in borderline cases is that of confusing syph ilitic osteochondritis of the knee with tuberculous white swelling History and regional findings in the joint itself should be subordinated to a complete general examination of every such case, including of course a routine blood Wassermann reaction. The local pictures in the two conditions may be practically indistinguishable. Sinus formation, sequestra, ankylosis may be late features of the syphilitic as well as the tuberculous process The blood Wasser mann reaction may be completely negative in syphilitic arthritis and yet therapeutic restoration be rapid and satisfactory (Fig 595) Absence of fever relative painlessness, preservation of the mobility of the joint and absence of local adenopathy all tend to suggest syphilis. Skinner directs attention to the value of repeated radiographic studies of joints under therapeutic test for syphilis. Within a few weeks the response of a syphilitic joint is readily dem onstrable in the plate, while that of a tuberculous joint is slight or absent. Here again the nonspecific arsphenamine factor may temporarily confuse the outcome. As in Figs. 607 and 611 the correct interpretation of cutaneous syphilids associated with the bone or joint lesion may make all the difference between correct and incorrect diagnosis. The association of a tuberculid such as lichen scrofulosorum with an aphlegmasic joint or a hydrarthrosis, as in Fig. 609 may on the other hand, have almost pathognomonic value in identifying as tuberculous a joint which might otherwise have been considered syphilitic. The resemblance of lichen scrofulosorum to the grouped follicular secondary syphilid must not be forgotten (Chapter XII)

In the differentiation of syphilitic from tuberculous tenosynovitis the commonly mentioned criteria of bilateral character in syphilis and failure of the process to involve surrounding tissues have not been sufficient. The concomi tant partial positive blood Wassermann occasionally seen in tuberculous processes and their response to arsphenamine must not be forgotten. The identification of a tuberculid will at times prevent an erroneous diagnosis of syphilis, a statement that applies to a variety of arthralgias and myalgias as well as to the more outspoken lesions. A tuberculid of the fingers (Fig. 542) may aid in identifying and correctly interpreting a bilateral tenosynovitis which will disappear under the nonspecific effect of arsphenamine therapy The differentiation of syphilitic from tuberculous involvement of bones of the skull is mentioned on p. 776

Confusion of Osseous Syphilis and Round-cell Sarcoma.—The erroneous diagnosis of sarcoma in syphilitic lesions of bone and periosteum was undoubt edly much more frequent in the past than at the present time with the wider application of the Wassermann test (Fig 578) One of us (J H. S) recalls vividly a case presented in 1914 before one of the larger dermatological societies of this country in which a young woman had been reduced almost to a

torso by successive operations for the removal of supposed sarcomas of her extremities. Finally when a crutch had replaced one leg and she was all but armless, an interstitial keratitis, veritable dispensation of Heaven in her case made the correct diagnosis unescapable. Even so small a group of cases as that here reviewed, contained two such errors in diagnosis, one of them well illustrating the fact that the ablest diagnosticians and competent pathologists may be deceived by this source of error

Additional cases of this sort are scattered through the literature (see Cabot Case [illegible], New England Med. J 1940, Westermark and Hallerström, 1937 Ungerman, Vicary and Eldridge, 1938). These latter authors point out that, while it is characteristic of syphilis that bone production exceeds bone destruction (see section on roentgenologic factor in diagnosis p. 774), when



Fig. 578 —Deposition of new bone in the soft tissues in osteosarcoma, the most distinctive single feature of the roentgenographic picture.

syphilitic involvement of the cortex occurs without involvement of the medulla or periosteum, the roentgenographic evidence may be solely of bone destruction without the characteristic bone production. When the periosteum is involved there may be a marked similarity between syphilis and sarcoma, the principal difference being that the periosteal reaction from sarcoma is more in the nature of an irritative reaction with new bone striae perpendicular to the axis of the shaft. In syphilis the new bone formation, as shown by the roentgenograph, is more laminated, the laminations lying parallel to the shaft and tending to unite with it at the margins of the process

In our experience mistakes of this kind arise from too implicit reliance on clinical signs, with neglect of the routine Wassermann test too credulous acceptance of the results of the frozen section biopsy from tissue removed by an operative incision for diagnosis and from the fact that the rapidly destructive processes of sarcoma as shown in the roentgenograph, may under certain

circumstances as just stated be simulated by syphilis. Systematic and invariable application of the blood Wassermann test before exploration would reduce the percentage of avoidable error in this field almost to the vanishing point. The apparent confusion of the microscopical pictures of gumma and sarcoma, may be due to the rich round-cell infiltration of the early gumma. The perivascular distribution of the infiltration in gumma and the presence of plasma cells even in the earliest cases, should arouse the suspicions of the careful observer. That the combination of radiologic and clinical findings exclusive of the Wassermann result may fail to make the correct diagnosis is apparent in Figs. 96 and 617. Roentgenologic study of other bones than the one under dispute may in doubtful cases cast some light on the situation by identifying a more distinctly specific but asymptomatic lesion elsewhere. The fact that osteogenic sarcomas metastasize early to the lungs should likewise not be lost sight of in looking for differential diagnostic clues. Most of the therapeutic tests were negative in Wassermann-negative disputed cases referred to the Syphilological Section for opinion. If the Wassermann reaction be positive and the lesion appear none the less to be sarcomatous, an arsphenamine therapeutic test is quite specific and can be rapidly given. It should be borne in mind in general however that it is better on the whole to call a syphilid a sarcoma than to allow a sarcoma to progress to inoperability in a leisurely mercurial or iodide therapeutic test for syphilis.

Malignant Metastases to the Bones.—These must be considered among the differential diagnostic possibilities of bone syphilis. The frequency of invasion of the bones of the pelvis and thighs by carcinoma of the prostat and of the spine by cancer of the breast are well known. Ovarian, renal and thyroid malignancies not infrequently metastasize to bone. Metastases of carcinoma t the vault of the skull are usually late enough and associated with enough collateral evidence of the primary origin to identify them. The presumption in cranial osteoporosis lacking obvious signs of malignant origin is, therefore, in favor of syphilis. Metastases of hypernephroma, however which may appear comparatively early have in our experience caused confusion in 2 cases.

Confusion of Hemangio-endothelioma and Syphilis.—Hemangio-endothelioma or angiosarcoma, mentioned in connection with the diagnosis of cutaneous syphilids, is likewise source of error in the diagnosis of osseous syphilis because of its attack on bone (Fig. 616). The identification of angiosarcoma or endothelioma of this type is discussed on page 710.

Confusion of Syphilis and Multiple Myeloma.—Moore has given us the details of case in hich multiple myeloma producing lesion simulating gumma of the sternoclavicular articulation was confused with syphilis until the Bence-Jones protein was discovered in the urine.

Hodgkin's disease, through its occasional invasion and destruction of bone may also cause confusion in diagnosis (Dresser and Spencer 1936) and the proliferative changes of isolated lesions of atypical Paget's disease (osteitis deformans) may cause diagnostic error particularly hen are concerned with early lesions radiographically demonstrated (Cophey 1941, Alexander and Schoch, 1948)

Confusion of Certain Cardiovascular and Osseous Lesions.—The symptomatic resemblance between the precordial pain of angina pectoris (coronary sclerosis) and the pain of osteoperiostitis of the sternum and periostitis of the left humerus may be confusing. While the pain of angina is the more spasmodic, it is well to make careful palpation for periosteal tender points, along the sternum at the sternochondral junctions for edema and points of tenderness, and for pressure pain over the humerus, with radiologic study if indicated. Aneurysm presenting through or bove the sternum, or t the sternoclavicular junction, may be confusing, for an neurysm incarcerated or containing clot may not pulsate. Even fluoroscopic examination may fail to disclose pulsation. Careful study of the physical signs may be necessary to prevent mistakes. Radicular pain due to aneurysmal pressure may cause erosions of the vertebrae due to pressure to give the external impression of Pott disease, thoracic or lumbar and periostitis of the ribs may be simulated likewise. A very careful study of the physical signs may be necessary to prevent hasty diagnosis of tuberculous spondylitis. In the same way the pain of subdiaphragmatic aneurysm may be confused with radicular pain secondary to hypertrophic changes in syphilitic spondylitis or t pressure caused by destruction of the vertebrae In thoracic and abdominal

aneurysms the fluoroscopic examination will usually assist in identifying the pulsating tumor but in subdiaphragmatic aneurysm the liver shadow may so obscure the findings that the diagnosis becomes at times extremely difficult, and depends on the detection of bruit, pulsation, and collateral signs. Aneurysm of the popliteal artery unless the bruit and pulsation be searched for may be misleading

"Syphilitic Pseudo-arthritis Deformans."—A modified arthritis picture calling for careful diagnostic interpretation is that of so-called syphilitic pseudo-arthritis deformans described by Mericampe, Fournier Dumesnil, and others. This picture has gathered form largely about the coincidence of a positive Wassermann test, and favorable reaction to treatment for syphilis with arthritis deformans. There seems to be little of specificity in the joint picture. Three of the most typical cases we have seen developed mental symptoms, and one of them was found to have a paretic spinal fluid. Psoriasis was coincident in several cases, and was especially marked in the patient who was discovered to have an early paresis. These patients have secured improvements in their arthritis under treatment for syphilis ranging as high as 65 per cent, but none has been

Fig. 579

SUMMARY OF DIAGNOSTIC MAXIMS IN THE CLINICAL DIAGNOSIS OF SYPHILIS OF THE SKELETAL SYSTEM

1 Have blood Wassermann test on every bone or joint case.
2. Examine the patient completely—not merely the lesion. Syphilis eludes the partial or subjective examiner
3. Suspect especially tibial, cranial bone and shoulder girdle lesions of being syphilitic.
4. In early cases much pain, little structural change suggests syphilis.
5 Remember the point of exquisite tenderness over early periosteal lesions.
6. Nocturnal pain is significant, but not infallible or invariable.
7 A roentgenogram is indispensable, but not infallible It ranks next t the blood Wassermann test.
8. Do not operate or incise for diagnosis until the Wassermann report is at hand.
9 Suspect syphilis in the won t heal" syndrome, whether spontaneous or after operative interference
10. The abnormal but mobile or hypermobile joint should arouse suspicion.
11 Watch neurologic signs and symptoms, especially pupils, reflexes, impotence bladder signs, lightning pains, and slight taxia with eyes closed or after dark.
12. Suspect bilateral hydrarthrosis, especially if recurrent.
13 Know the earmarks of heredosyphilis and apply the knowledge to every patient, young or old.
14. Know cutaneous syphilids and their scars Never lightly dismiss destructive skin lesion or scar associated with bone or joint disease. Concomitance occurs in as high as 40 per cent.
15. Look for tuberculids as well as syphilids in association with bone and joint pathology
16. Recall the nonspecific effects of treatment for syphilis, especially with arsphenamine on some periosteal processes, infectious arthritis, tuberculosis.
17 Never think of tuberculosis, sarcoma, or "rheumatism without thinking of syphilis.

completely cured or even permanently relieved, which leads to the inevitable suspicion that the effect was rather a nonspecific one upon the systemic infection background of an arthritis deformans than upon syphilis as the sole cause of the condition.

Nonspecific Periostitis.—Periostitis as a nonspecific diagnosis raises the question as to whether there is any response on the part of nonsyphilitic periosteal lesion t treatment for syphilis undertaken as a diagnostic test. Uncertainty in regard to this question as the occasion for several erroneous diagnoses in our earlier experience with bone lesions, as shown in the case histories. A nonspecific periosteal lesion may present distinctly the yelling of syphilitic periostitis, and the response of the pain to a single injection of arsphenamine may be immediate and complete (Fig. 585), yet no evidence of syphilis be found after the most painstaking and repeated investigation with observation of the patient and his family over a period of years. While this phenomenal response is not common, the frequent use of blue ointment, for example as nonspecific treatment for osseous lesions lacking evidence of syphilitic origin suggests that these cases would be found on fuller study to be a definite and not unimportant group among the factors of error in diagnosis.

Rost (1942) has called attention to the roentgenographic manifestations of the bone involvement from Bejel (endemic syphilis as observed in the Euphrates river valley). The picture described is similar if not identical to the proliferative and periosteal and endosteal changes described as resulting from late acquired syphilis. Bone changes as seen in early congenital syphilis and as associated with the neurotrophic joint are thought not to occur.

THE TREATMENT OF BENIGN LATE SYPHILIS (OSSEOUS AND CUTANEOUS)

The treatment of acquired late syphilis of the bone and of late cutaneous syphilis is essentially similar It is, as a rule, simple and successful if the process be an actual active syphilid The exceptions include those lesions which have recurred in nonregenerative bone, such as the skull, or which involve trophic factors such as the tabetic arthropathies. Superficial structures which have been destroyed by the disease likewise cannot be restored though healing takes place with the arrest of the active process and the development of a characteristic scar Old and neglected syphilids of the bones which have been heavily secondarily infected or repeatedly subjected to operative or traumatic insult, and occasionally the bone lesions of so-called malignant or highly resistant syphilis, may prove refractory to treatment. Sequestra, when they occur may offer temporary impediments to complete recovery and require surgical intervention for their removal

Fig. 580.

RESULTS OF TREATMENT OF 250 PATIENTS WITH BENIGN LATE SYPHILIS
(after Wasserman and Goodman, *Am. J Syph. and Neurol.* 18: 458, 1934).

Amount of Treatment	Percentage Results			
	Blood Serologic Test		Clinical Outcome	
(arsphenamine and heavy metal, 6–8 injections per course)	Wass. fast	Wass. Reversed	Satisfactory	Relapse
One course or less	68.8	19 7	68.2	31.8
Two to four courses	47 1	44.1	86 9	13.1
More than four courses	49.3	31.5	94 6	5 4

The following discussion is based upon 108 cases (Fig. 581) observed in the Mayo clinic series and on Wasserman and Goodman s (1934) excellent report of 250 cases followed from two to fifteen years (average five years)

Treatment of Uncomplicated Benign Late Syphilis.—Late cutaneous or osseous syphilis is almost never encountered in patients who have had adequate treatment for early syphilis. It may be assumed, therefore, that benign late syphilis may be prevented for the most part by the adequate treatment of early syphilis.

The plan of treatment for uncomplicated osseous or cutaneous syphilis need make no provision for an injurious Herxheimer reaction or for the therapeutic paradoxes discussed under *visceral and vascular syphilis. It will be re*membered however that coexisting syphilis of other systems in about one fourth of these cases is more serious than is involvement of the skin or the bone In these instances initiation of treatment too rapidly may be contraindicated. The management of benign late syphilis, as with all other phases of the disease requires complete appraisal of the patient and the immediate institution of arsenical treatment only if vital structures and systems are not involved.

The delayed Herxheimer reaction in bone lesions has been mentioned, and may give a deceptive impression for as long as two or three weeks that the patient is getting worse (Fig 617) This is true rather of later lesions than of earlier ones, in which the relief of pain and the rapidity of regression even in a marked hydrarthrosis or synovitis is sometimes almost miraculous. Complete subsidence of the active process may be expected in from one to three courses, except in syphilis of the palate and septum in which extraordinary resistance is sometimes encountered requiring years of heavy metal and iodide. In treating patients with osseous syphilis, it is important as in all aspects of the disease, to envisage the entire process and to treat for arrest of the infection, not merely for symptomatic relief of the bone lesion. This will seldom require less than four to five courses of 6 to 8 arsphenamine injections each, within a year and a half 40 to 60 bismuth injections *ad interim* and following the arsenical.

Wasserman and Goodman have pointed out that with bone lesions of the proliferative type, it is the exception rather than the rule t note any appreciable change in the roentgenograph as result of treatment even though the active progress of the lesion has been arrested. If the syphilitic process has been predominantly destructive, on the other hand, treatment will usually result in roentgenographic evidence of repair Interruption of the bone structure is usually perma-

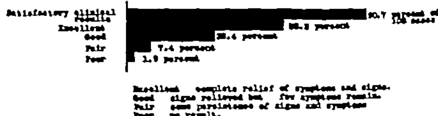


Fig. 461

nent and increased density results from deposition of calcium in the diseased area, over period of years, rather than in a regrowth of vitalized bone.

Management of Resistant Osseous Syphilis.—In the management of resistant osseous syphilis we have seen some of the best examples of the superiority of the coincident administration of heavy metal and arsphenamine over their alternate use

The effect of rest and increase of general resistance is apparent in the old processes, in which secondary infection is often more serious as an obstacle to healing than the syphilis as such Cases of this sort include patients with the tibial osteomyelitis and positive blood serologic reactions that one meets on the wards of charity hospitals, who never accumulate sufficient resistance to shake themselves free of their combination of handicaps.

Resistant Positive Serologic Reactions in Osseous Syphilis.—The resistance offered by the blood Wassermann reaction in 63 patients who received three or more courses of arsphenamine treatment with interim heavy metal is of interest. Fifty per cent remained persistently positive in both the Mayo Clinic and the Wasserman and Goodman series. Individuals who develop negative blood serologic tests as a result of treatment of benign late syphilis

Moore calls our attention to the value of the increased pai of Herxheimer reaction as a means of directing attention to the involvement of other bones not previously recognized.

are apparently no less likely to relapse clinically than those whose Wassermann remains persistently positive. It may be assumed, therefore, that the clinical outcome (satisfactory or unsatisfactory) is not dependent upon the serologic response to treatment. The object of treatment is symptomatic relief the healing of lesions, the avoidance of progression or relapse in any structure in the body and the prolongation of life in those in whom there is

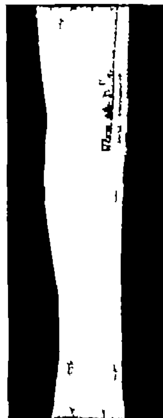


Fig. [illegible].—Periostitis of the tibia in woman whose chief complaint was aching pain in the lower leg. The blood Wassermann reaction was positive. The response to treatment was prompt, but spinal fluid examination year later showed latent neurosyphilitic involvement which it required another three years to reduce to normal. She has been under observation seven years, and is apparently well. The mere discovery of syphilitic bone lesion, and symptomatic relief under treatment, should not discourage the complete study of the patient for evidence of other types of syphilitic involvement. Treatment should be directed at the most serious type of involvement found and not merely at the bone lesion.

associated involvement in the vital structures. This will require the maximum treatment outlined above.

Four fifths of relapses when they occur will be within six years after the cessation of therapy (average 5 1 years) will usually be of the same type as the initial lesion and in the same structure but not necessarily at the same location.

Surgical Treatment of Gummatous Osteitis of the Skull.—The treatment of gummatous osteitis of the skull, of the Charcot joint, and of the long bone

lesion with sequestrum offer special therapeutic problems, with an important surgical aspect. Gummatous osteitis of the skull, involving extensive necrosis, heals with the greatest difficulty the dead bone preventing the restoration of the soft tissues of the scalp above it. Adson has described a method used in some of our cases, in which the necrotic bone of the outer table, or if necessary even deeper is removed with a chisel until free bleeding occurs. Granulations then develop and epidermatization occurs if the edges of the healed scalp wound are freshened or grafts made It goes without saying that systematic treatment for syphilis should precede and follow this measure.

Palate and Septum.—Necroses of the bones of the face offer at times very difficult problems, and extensive operations may be necessary to remove

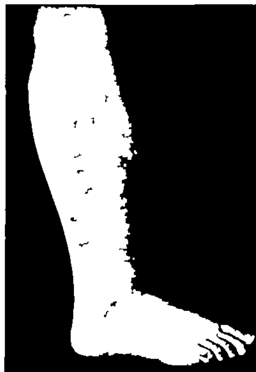


Fig 483.—The enormously hypertrop... ...s of ...syphilis producing picture suggesting so-called "nonsuppurative osteitis of the tibia. This patient was young girl ...th strongly positive blood Wassermann reaction.

sequestra whose suppurative accompaniments may drain into the frontal and other sinuses, maintaining a continuous and resistant pyogenic infection. Such patients have in our experience shown a special susceptibility to cutaneous irritability and reaction under treatment, possibly merely coincidental, but again perhaps due to the chronic infection of which they are victims.

Avoid Incising Sca p Gummas.—A caution is perhaps valid in connection with the tendency to incise nodules in the scalp Surprising resolution will sometimes follow vigorous treatment in patients with gummas of the skull and scalp that have not been exposed to secondary infection and retraction of the scalp tissues by early incision. We believe it to be wise therefore to delay drainage of even softened nodules as long as possible, and to limit such drainage as is d ne to the smallest possible openings.

Fig. 864.

A CASE OF OSGOOD'S (SCHLATTER'S) DISEASE OF THE TIBIA SHOWN BY OBSERVATION OPERATION AND INVESTIGATION TO BE OSSEOUS SYPHILIS

A railroad man, aged thirty-four

Examined 2/3/19.

Chief Complaint Poor extension of the left knee of fourteen month duration.

History Swelling of the entire knee without previous injury Reducible by poultices and rest. Fluid aspiration six months ago. Pain and limitation of movement has persisted. No history of syphilis. Gonorrhea at twenty-two.

Examination Heat and swelling t insertion of ligamentum patellae. Pain and marked weakness on extension. Area affected was the size of fifty-cent piece. Heart slightly enlarged to left. Urine negative. Blood Wassermann reported negative, but *clears slowly* Roentgen-ray report, Osgood' disease Avulsion left tibial tubercle.

Consultant's Diagnosis:

"Osgood' disease left tibial tubercle. Explore and trephine and follow with stiff legged brace for two months.

After Operation. Relief and fair comfort for four months. Six months later lump recurred in the region of previous operation with pain and limitation of movements.

Re-examination Slight enlargement and irregularity of head of tibia. Slight roughening of left anterior aspect of upper tibia. Advised re-examination in one year.

Re-examination: Fifteen months later Pain and soreness, middle and inner aspects of left tibia. Pain is severe, sharp, and shooting Relief by hot packs. N history of injury Diffuse thickening and enlargement of tibia. Roentgenogram Bony overgrowth from the outer aspect of the outer tuberosity Slight periostitis near the border of the tibia. Probably old osteomyelitis. Leukocytes 8900. Blood Wassermann test negative.

Second Operation Tumor of the upper end of the tibia cartilaginous and resembling exostosis. Area near the border of the middle third of the tibia explored. Periosteum thickened and bone hard, but in the middle of this area was granulating portion which was chiseled aw y entirely

Pathologic Examination Tissue removed at operation showed marked perivascular infiltration and fibrosis. Occasional foreign body giant-cells ere found. Send for syphilologic investigation.

Serologic Results: Three positive and two clears slowly Wassermann reactions in 7 tests. Spinal fluid negative.

Therapeutic Test Arsphenamine and mercury Marked improvement. Mobility of knee completely restored.

Discussion

At the time this patient was first seen it was not generally understood that clears slowly report on the Wassermann reaction (delayed negative) is in all probability positive Wassermann result. Had this been known the syphilitic factor in the picture ould have been earlier recognized.

The development of new bone complications *in situ*, like the refusal to heal after operative trauma, unless malignancy is suspected, is suggestive of syphilitic factor, and should lead t investigation before a second operation is undertaken.

The provocative procedure showed the blood Wassermann reaction to be definitely but not strongly positive.

There is again a possibility that some of the effect of treatment for syphilis was nonspecific, for there was marked focal infection of the tonsils.

The pathologic picture of the tissue removed supports the diagnosis of syphilis, as established by the provocative test.

Since one operation had merely resulted in extension and more serious involvement, the treatment is probably responsible for the permanent good result after the second.

Is avulsion of the tibial tubercle necessarily due to syphilis? Of course it is not. The syphilitic process probably appeared upon prepared soil.

Management of the Charcot Joint.—The Charcot joint should not theoretically if it is a pure trophic degenerative phenomenon, respond to treatment for syphilis. On the other hand it does at least show symptomatic improvement in our experience. A brace or an amputation is too often the only therapeutic proposal when intelligent treatment for the neurologic condition would have increased the patient's comfort and effectiveness and arrested the progressive spinal degeneration. Treatment for tabes should not, therefore, be withheld even if there are negative serologic findings. O'Leary (1938) as spokesman for the Cooperative Clinical Group found that of 43 cases of Charcot joint followed two to twenty years, 7 per cent improved and 56 per cent remained stationary as a result of treatment giving a total of 63 per cent in which progress of the disease was arrested

Treatment is not necessarily however offered as a preventive of Charcot joint and the patient cannot be assured that it will stop the development of multiple joint involvement. In 37 per cent of the C C G group of cases there was progression in spite of antisyphilitic therapy In general the physical changes of the Charcot joint, when well advanced are not in the least affected by treatment for syphilis The accompanying trophic ulcer of the toe or foot (mal perforans) however may occasionally heal even though the joint is not affected

Mechanical support with a hinged brace is, as a rule, the only palliative to offer the patient with a well-developed Charcot knee or ankle So long as the joint is reasonably rigid or the patient manages to adapt it to his needs, amputation may be postponed If however the joint becomes a seat of infection a rapid decline in the general condition of the patient follows, often out of all proportion to the apparent severity of the joint condition. In such cases amputation as soon as the process can be brought to quiescence with hot dressings has in the cases we have observed had excellent effect.

Weinberg (1930) Key (1934) and Epstein (1936) have summarized the orthopedic treatment of Charcot joint. Pomeranz and Rothberg (1941) feel that the value of surgical fusion or stabilizing operations for this disease as described by Cleveland and Smith (1931) Cleveland (1935) Seto-Hall (1938) and McCauley (1939) hardly justifies optimistic claims. They stat that no hip joint can be successfully fused and that the end results of fusion of the knee can be determined only as result of prolonged observation. "Several of our cases which were considered successfully orthodesed, subsequently 'unfused' after months or years. (In one case seven years)

Casts.—The premature application of a cast in cases with syphilitic hydrops of a joint has seemed at times actually to delay the progress of the case partly no doubt, because the cast was applied in ignorance of the correct diagnosis and as a substitute for specific treatment. It has sometimes been necessary to take more trouble to reeducate such patients to the use of their limbs after removal of the cast than would have been required had systemic treatment been allowed to meet the situation unaided.

Removal of Sequestra.—Removal of sequestra in syphilitic bone lesions should not be undertaken until the patient is well under the influence of treatment for the operative provocation simply extends the syphilitic process, often with more sequestrum and repeated operation. The vicious effect of such a cycle was seen in the astonishing hypertrophic changes of the much operated syphilitic tibia in a woman of forty-seven. The bone had almost reached the dimensions of the patient's forearm after nine operations and "scrapings." Her hereditary infection had been neither diagnosed nor treated.

DRY CLINIC ON BONE AND JOINT SYPHILIS

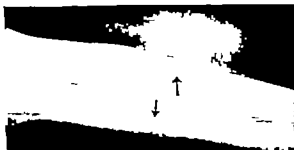


Fig. 583

PERIOSTITIS AS A DECEPTIVE SIGN OF SYPHILIS

A male aged thirty-one, married.

1915 Backache relieved by baths.
1916 Aching Pain Right Thigh and Knee, Constant, Worse at Night. One Year's Duration.
- Wf and 2 children well. No miscarriages.
- No history of syphilis, primary or secondary or of gonorrhea. Exposure admitted.
- Robust male. Never been ill.
- SWR negative June, 1916.
- Roentgenogram of right femur periostitis, lower half.
- Provocative injection neoarsphenamine 2 dg.
- Pain Disappeared Within Twenty-four Hours and Has Never Reappeared.

1916 Provocative series of Wassermann test negative throughout.
- Wife Wassermann negative.

1917 Eight injections neoarsphenamine 3 to 6 dg 20 injections mercury salicylate gr 1 to 2 intramuscularly

1918 SWR negative
- Cerebrospinal Fluid—SWR negative Nonne negative, 15 lymphocytes.
- Neurologic Examination Pupils slightly oval.
- Anal and abdominal reflexes reduced.
- Epigastric and testicular tenderness reduced.

1921 SWR negative.
- CSF negative (1 lymphocyte).
- Pupils as above.

Discussion

1. Nocturnal bone pain, with the x-ray picture of periostitis, constitutes strong evidence for syphilis in spite of the negative serology. The immediate and permanent relief of the pain by the first arsphenamine injection is even more suggestive. A pleocytosis of 15 cells in the spinal fluid in a healthy person even with trivial neurologic signs, after two years of observation and treatment, is contributory evidence of syphilitic infection. Taken alone, however it has little weight.
2. None of this evidence, however can be rated as conclusive, especially in view of the evidence cited for nonspecific effect of treatment for syphilis on nonsyphilitic bone processes.
3. A reexamination of this patient five years after his first examination, and of his wife, discloses no evidence of syphilis in the latter nor of activity in the former
4. Did this patient have syphilis? It is impossible to give a conclusive answer.
5. Periostitis of any type cannot be accepted unqualifiedly as evidence of syphilis, but it justifies at least a blood Wassermann test and often fuller investigation.
6. In this case the existing uncertainty would, if treatment were begun at all, justify complete therapy with prolonged observation. Otherwise the patient might be left with impaired resistance, prepared for some form of relapse. For meaning of effective treatment see Fig. 580. This patient would not cooperate to that extent.



Fig 586.—Gummatous involvement of the sternoclavicular articulation and upper end of the sternum, for comparison with Fig 587 (aneurysm) B shows the effect of treatment. While the signs of aneurysm are usually pronounced enough to prevent mistake incarcerated or clotted aneurysm may not pulsate, and exploration or incision may be considered. It is almost as serious to begin routine intensive treatment for syphilis on cases of this kind without eliminating aneurysm, for the effect of arsphenamine on patients with aneurysm, especially at the outset, may be disastrous.



Fig 587 —Aneurysm of the aortic arch, presenting through the upper end of the sternum Compare with Fig 586. The infection was of twenty-five years duration and the signs of aneurysm obvious enough to preclude error The substernal dulness was 18 cm. across. The pain of mild angina pectoris and aneurysm and that of osteoperiostitis of the sternum and humerus may be confused.



Fig. [illegible].—This patient, aged sixty-three years, gave history of penile lesion forty years ago. Throughout long and active life he had been absolutely free from any symptoms of the disease. His only complaint at the time of examination was swelling of the right side of the neck of one year duration with occasional slight tenderness. The blood Wassermann reaction was repeatedly strongly positive. Spinal fluid was negative. H had never had any treatment for syphilis. Roentgenographic study as practically negative. The patient was given mixed treatment by mouth and warned not to allow any young medical enthusiast to try modern treatment methods on him. The lesion as apparently gumma and by subsequent report promptly disappeared.



Fig. [illegible].—This patient was sent for syphilological examination because of the presence of bone lesion in the "suspicion-arousing region of the shoulder girdle and upper sternum. The tumor was smooth, firm, not tender and had been present, though smaller, for many years. Of late it had grown more rapidly The patient could give no history of syphilis, though he admitted frankly that he might have been exposed. A tentative diagnosis of chondroma had been made, and he was advised not to undergo operation. He was so conscious, however of the fact that such lesion might suggest syphilis, that he insisted upon operation. The lesion proved to be sarcomatous, and postoperative hemorrhage cost him his life. Not every enlargement at this point is syphilitic in origin.

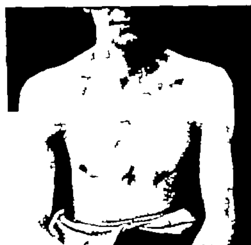


Fig 490.—This woman t fifty years of age began to show signs of a general breakdown. It was presently found that she had hypertension, that the aorta showed aneurysmal dilatation, that there was some myocardial insufficiency and that the blood Wassermann reaction was strongly positive. On examination, note was made of the enlarged right sternoclavicular articulation. It was the sign upon which surgeon of the past generation had evidently based diagnosis of syphilis long before the day of the Wassermann and given her drops. She was never informed as to the situation, and went on to lat complications, again in accordance with the syphilological technic of her day. Her children are apparently normal. She has since been asked by physician when her collar bone was broken. Under conservative but thorough treatment she ha reached her seventieth year

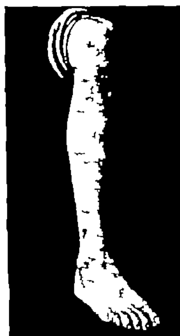


A B C

Fig 491.—This patient is veritable parade ground for osseous syphilis. His chief complaint was rheumatism and loss of voice. The laryngeal condition came on suddenly after shouting and consisted of double fixation of the cords in slight abduction, possibly due to gummatous infiltration. The bone condition caused him less concern. He presented osteitis and periostitis of the left parietal bone, both clavicles, both scapulae all the sternochondral junctions, and dorsal spondylitis. The tumor formed when the gummatous lesion of the skull developed, was promptly lanced by physician, without Wassermann test. The clavicular process was initiated by injury. The massive thickening of the clavicles and scapulae was astonishing. The blood Wassermann reaction was positive. Further study could not be carried out, and the patient could not remain for treatment.



A



B

Fig [illegible].—This young man (aged thirty-two) gave his chief complaint as "stomach trouble which had inspired the needless surgical intervention shown by the abdominal scar In his preliminary examination very little of importance appeared, but his blood Wassermann reaction, routinely taken because of his age, was returned as positive. His case was then reviewed, with the discovery that he had greatly thickened saber tibiae, the right one showing the scars which the patient then recalled as having been due to operative scraping of the bone in childhood. Through failure completely to strip the patient in his first examination, these almost pathognomonic tibiae had been overlooked, and only the routine Wassermann test saved the diagnosis. On examining A, visible ground for suspicion, independent of the tibiae, can be readily recognized. This patient weighed 138 pounds. His clavicles, especially the inner third, would have suited man of 200 pounds weight. There was marked old osteoperiostitis with changes demonstrable by roentgen-ray The patient apparently had congenital infection. His surviving parent declined examination. The stomach symptoms completely disappeared after treatment, though the stomach roentgen-ray was negative, and there was no evidence of neurosyphilis.



Fig 593

SYPHILITIC PERIARTICULAR ARTHRITIS FOLLOWING TRAUMA WASSERMANN NEGATIVE. THERAPEUTIC TEST POSITIVE.

Boy aged nine.

Chief Complaint "Broken left elbow Fell down stairs seven weeks ago striking left elbow on banister No symptoms until two days later Aching of elbow joint.

X-Ray Diagnosis Fracture? Placed in cast, with subsequent manipulation under anesthesia.

Examination Arm placed at right angles, slight motion, some effusion but the joint with palpable thickening X-Ray shows slight periostitis lower end of femur with erosion of articular surfaces.

Patient otherwise negative except for left internal strabismus and congenital cataract.

Syphilologic Examination: Mother had 8 miscarriages following this child.

SWR negative direct and on provocative.

Therapeutic Test: 6 arsphenamin injections 1 to 8 dg and 30 inunctions. "Beautiful result. Swelling disappeared, mobility largely restored.

After another 40 inunctions full motion restored and no effusion.

Father denies syphilis, refuses examination. Took the patient home without final advice.

Discussion

1 The x-ray changes (second examination) can hardly be regarded as absolutely specific.

2. This is as good an example of Simon-pure therapeutic test as one usually finds. Examination of the spinal fluid was not permitted. The mother history of miscarriages, even though they followed the child' birth, wa valuable clue. The child showed no stigmas of heredosyphilis. His infection probably occurred at birth or in early childhood.

3. No better example of the effect of trauma in producing flare-up of quiescent syphilis t point of lowered resistance could be desired.

4 **Whenever an Unfavorable Reaction to Injury is Out of All Proportion to the Gravity of the Injury or th Seriousness of th Exciting Cause Suspect Syphilis, Especially If th Onset of Reaction Symptoms is Delayed.** This boy fell down three steps, with bump on the elbow that was of so little moment that symptoms did not begin for three days following the injury



Fig. 504.—An aviator bumped his knee in leaving his machine. Thereafter it was persistently sore to touch and painful on movement. The x-ray showed inflammatory changes in the bone of the internal tibial tuberosity that led to the taking of a blood Wassermann test, which was strongly positive. Recovery was immediate under treatment for syphilis.

Fig. 505.

SYMMETRIC SYNOVITIS OF BOTH KNEES IN THE COURSE OF NEUROSYPHILIS RELIEVED BY ARSPHENAMINE TREATMENT. PROBABLE NON SPECIFIC EFFECT. BEGINNING CHARCOT JOINT(?)

A married woman, aged twenty-eight.

Examined 2/16/19

Chief Complaint Headache, gastric distress. No history of syphilis.

Examination Wassermann reaction on the blood was strongly positive. The spinal fluid Wassermann was strong positive with positive Nonne, 40 lymphocytes, gold sol 0055545443. Osseous system negative. Favorable response to treatment. Note that there was no osseous disturbance at the outset.

Treatment Following the first course of arsphenamine treatment patient went home, neglecting the removal of three abscessed teeth. She began inunctions and became stiff in the joints, sick, and confined to bed. The abscessed teeth were then removed, with recovery. One year later the knees enlarged symmetrically three weeks after a fall. A large amount of fluid was aspirated by her physician. Returned for examination. Clinical appearance of the knees suggested Charcot joints. Marked synovitis, moderate effusion of both knees, crepitation. Radiogram negative. Arsenical therapy was resumed. The synovitis cleared up immediately although already of four months' standing. Dr Henderson suggests the hydrops is possibly a symptom of an early Charcot joint.

Discussion

On two or three occasions in patients with syphilis synovitis of this type improved remarkably under treatment, but in at least one case the joint later developed Charcot changes in association with neurosyphilis.

This patient had had, however, mercurial arthritis, and on this occasion there was some suspicion that the entire picture was that of an infectious multiple arthritis rather than syphilitic process.

Great care must be used in interpreting the action of arsphenamine on arthritis as demonstration of syphilitic origin. Nonspecific effects are quite common.

The amount of treatment which this patient had had previous to the synovitis would seem to make syphilitic multiple arthritis impossible.

Note that she came originally for "stomach trouble," which was found to be referable to neurosyphilis.



Fig [illegible]. (See next page.)

Fig. 506 (*Continued*)

HYDRARTHROSIS OF THE KNEES (CLUTTON'S JOINT), JUVENILE TABES, AND STIGMATA OF HEREDOSYPHILIS. VALUE OF A COMPLETE EXAMINATION IN IDENTIFYING UNUSUAL TYPES OF OSSEOUS SYPHILIS.

A schoolboy aged twelve.

This boy's syphilitic infection was brought to our attention incidentally to the diagnosis of his mother's case.

In the course of a routine inquiry as to the health of her living children she stated that her first child (this patient) had had his legs placed in casts for swelling of the knees. She remarked incidentally and without prompting that the pupils of his eyes did not seem to be of the same size. This at once aroused the examiner's suspicions, and when the child was subsequently seen he presented the following findings: Facies 80 per cent. Suggestive upper central incisors. Pupils unequal, irregular, left larger and fixed to light. Remains of old interstitial keratitis. Bilaterally symmetric hydrarthrosis of the knees (Clutton's joints). Spleen palpable. Well-marked sabering of the tibiae. Blood Wassermann reaction strongly positive. Spinal fluid Wassermann negative with 0.4 and 0.6 c.c., weak positive with 1 c.c. Nonne positive; 14 small lymphocytes. Colloidal benzoin 000,111 221, 000,000. Patient was placed on treatment as follows: First course: 6 arsphenamin injections, 2 to 3 decigrams each. Mercury succinimid intramuscularly 20 injections, ⅙ to ¼ grain daily. The plaster casts were gradually removed, and as the hydrarthrosis subsided the patient was able to walk about with crutches. Interim treatment 40 inunctions, four months interval. A flare-up of the interstitial keratitis occurred which subsided during treatment. Second course: Casts completely removed. Knees almost normal. Third course: 6 arsphenamin injections, 2 to 3 decigrams; 40 inunctions at home. Boy now in excellent general condition. No symptoms of any kind.

DISCUSSION

This case is an excellent illustration of the value of looking beyond the immediate presenting symptom or lesion for the etiology of the patient's condition. This boy presented a number of stigmas of heredosyphilis which would have made a diagnosis even without a Wassermann reaction. Symmetric hydrarthrosis of the knees as a manifestation of heredosyphilis is not as familiar to the profession at large as it might be. On the other hand, it is of interest to note that in this boy's case the onset was febrile so that the process might readily have seemed to be infectious in origin.

Symmetric hydrarthrosis of the knees without manifestations of heredosyphilis may occur, but as a rule the tuberculous or septic process may be distinguished by the presence of an arthritis which is absent in the typical Clutton joint.

A point of some interest in this boy's case is the fact that part of his pupillary rigidity was due to posterior adhesions of the iris margin to the lens and not to the true Argyll Robertson syndrome. There were, however, other signs supporting the diagnosis of neurosyphilis, including the spinal fluid findings.

Only a definite search of the familial history for evidence of syphilis in this mother's children brought this case under our observation. A Wassermann reaction had just been taken by the home physician, although the result had not been reported to the family.

In our experience it has not been necessary to place syphilitic joints in plaster if intensive antisyphilitic treatment be promptly applied. Symmetric hydrarthrosis in heredosyphilis is not necessarily confined to the knees, but may also involve elbows and wrists.



Fig. 497.—Gummatous osteitis of the skull, showing the irregular areas of bone destruction without proliferation.



Fig. 498. (See next page.)

Fig. 508 (*Continued*)

BILATERAL CHARCOT KNEES IN A BENIGN TABES

A man, aged forty-eight.

Examined: August 16, 1922.
Chief Complaint: Pain and disability affecting both knees.
History: In this patient general examination he denied syphilitic infection. When questioned later by the syphilologist he recalled genital sore thirty years ago which was burnt off without further treatment. He has always been in robust health until five years go, when his right knee as cut ith scythe Four months later swelling began, and six months later the knee as operated upon, the patella lifted up, and the trouble scraped out. He was told that it was tuberculosis. Three years later the left knee beg to swell. Four months after this both knees became obbly but the patient recalls that his right knee had wobbled before the first operation.
Examination Pupils unequal. Right larger than left. Right "frozen to light. Left sluggish. Both knees enlarged, marked lateral motion. Knee-jerks and nkle-jerks absent. *Ray of knees* Bilateral Charcot joints. *Eye examination.* Mild per iphoral chorioretinitis. Slight hypertension changes. Blood Wassermann reaction negative. Spinal fluid Wassermann negative, 0 4, 0.6, and 1 c.; Nonne negative; 4 small lymphocytes. Neurologic examination Tabes dorsalis.

DISCUSSION

In endeavoring to obtain history of syphilis it is well t question the patient more than once. H may recall something bet een times.

This patient gave typical history of lightning pains of fifteen years duration, but apparently no inquiry had ever been made regarding them.

The pupillary reactions and absence of deep reflexes were detectable upon ordinary physical examination. It is conceivable but not probable that they were normal at the time of the first operation.

The negative blood Wassermann reaction and negative spinal fluid is not unusual in tabetic arthropathies.

Not the extraordinary good health enjoyed by this patient without symptom of syphilis over long period of years.

The -ray and consistent search of every patient for the neurologic signs of tabes are the most effective means of diagnosing tabetic arthropathies.

The blood Wassermann reaction is no substitute for clinical signs in these cases especially

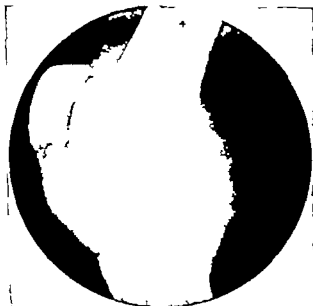


Fig. 509 —Typical Charcot knee (patient shown in Fig. 508)



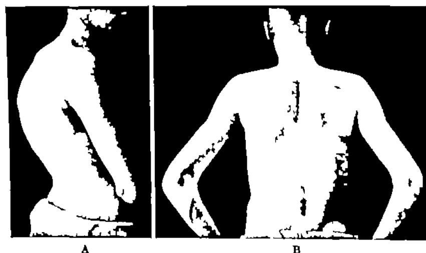
Fig. 507.—Gummatous osteitis of the skull, showing the irregular areas of bone destruction without proliferation.



Fig. 508. (See next page.)



Fig. 601.—Charcot shoulder with displacement of the head of the humerus from the glenoid fossa. (See Fig. 600.)



A B

Fig. 602.—The history and roentgen-ray findings on this patient are given on page 804

CHARCOT SPINE IN LUES HEREDITARIA REGARDED AS POSTURAL DEFORMITY

A schoolboy aged sixteen.

Examined 6/20/22.

Chief Complaint: Becoming round shouldered.

History: Onset one year ago. Painless. Regarded as due to faulty posture No other symptoms. Family and past history apparently negative.

Examination: Left pupil fixed t light. Right pupil normal. Marked lower dorsal kyphosis with slight lateral curvature in the lumbar region. Facies suggests lues hereditara. Knee-jerks absent. Roentgenogram. Scoliosis dorsal and lumbar spine Partial destruction body of eleventh and t elfth dorsal vertebrae Destruction body of first and second lumbar and fourth and fifth dorsal vertebrae. N muscle spasm, no limitation of motion. N pain on jarring Blood Wassermann reaction strongly positive.

Treatment: Six arsphenamine injections, no change in spine. Spinal fluid examination (second arsphenamine course) Wassermann strongly positive; Nonne positive; 100 small, 25 large lymphocytes, 10 polymorphonuclears gold sol 5555432100. Sixteen intravenous arsphenamine injections, three Swift Ellis treatments—spinal fluid reduced to normal after third arsphenamine course. Remarkable grow th and general improvement. N change in back. Gives mental impression of paresis, however Neurologic examination, juvenile tabes.

Discussion

Rapidly developing postural defect in young people here served as a clue t heredosyphilitic processes the spine and should not be lightly dismissed as merely postural.

This bone lesion, at first regarded spondylitis in view of neurologic signs and destructive changes, was later interpreted a Charcot spine in association with juvenile tabes. Rest in bed nd a brace had practically no effect on this lesion.

The spinal fluid is not that of the conventional long-standing juvenile tabes, but suggests rather that of a juvenile paresis. The patient mental make-up suggested early juvenile paresis, but the remarkable and complete response to intensive arsphenamine and intraspinal therapy rather weakens this supposition.



Fig. 603.—Roentgenogram of the Charcot spine of the patient shown in Fig 602.



Fig. 604.—The syphilitic bursopathy of Verneuil. Note the suggestive group of pigmented scars about the right knee in A. (Collection of Drs. Keidel and Moore.) In B (collection of Dr John E. Lane) the gummatous infiltration has broken down. A blood Wassermann test should be taken on all cases of chronic "housemaid's knee" before incision or removal of the bursa is attempted.

Fig. 605

SYPHILITIC SYNOVITIS OF THE LEFT KNEE. REPEATED ASPIRATION WITHOUT WASSERMANN TESTS, AND REPEATED RECURRENCE. NON-SPECIFIC OR SEPTIC FACTOR (?). PERMANENT RESULT FROM TREATMENT FOR SYPHILIS

Clergyman, aged thirty-five

Chief Complaint. Swelling of the left knee. History of iritis one year ago. Cleared up by 2 injections in the arm. Penile lesions seven years ago (history obtained later). Had marked rheumatism at the time. Four attacks of synovitis in seven years. Usually painless. No limitation of movement.

Examination. Obviously fluid in the left knee-joint. X-Ray negative. Calcareous spur right foot. Tonsils slightly septic. Three bad teeth. No blood Wassermann reaction taken.

First aspiration of left knee-joint. Injection 1 to 2 ounces iodoform in olive oil. Prompt recurrence synovitis.

Second aspiration 4 ounces fluid was removed—1 to 2 ounces iodoform in olive oil.

Recurrence aroused suspicion and history of iritis with response to intravenous injections led to taking of blood Wassermann reaction. Blood Wassermann reaction strongly positive. Placed on treatment with arsphenamin and mercury. Synovitis promptly disappeared. Did not recur.

DISCUSSION

The taking of a blood Wassermann test on every patient who has a bone or joint lesion, regardless of its character is a standing order for every diagnostic and surgical service.

A social criterion (clergyman) was responsible for the inadequate taking of the history of syphilis in this patient.

The story does not, however, lack evidence of a septic influence. The intravenous injections may have been phylacogens. There were, moreover, occasional recurrences of joint trouble affecting the fingers even after treatment for syphilis was well under way.

This patient proved later to have what seemed to be a neurosyphilis of the paretic type, but which at autopsy was found to be a frontal lobe glioma. The history of this phase is detailed in the chapter on Neurosyphilis. He had an undoubted syphilitic infection.



Fig 606.—This is fairly good example of the effect of incising gumma. Note the radial extension of typical group of serpiginous ulcers from the line of incision. The raised border momentarily suggests epithelioma, but it is fair test of the "instinct of student of syphilis to "feel" as well as see the elements in the gross appearance of this lesion that make syphilis almost unescapable *A positive Wassermann reaction should not be necessary in case like this to raise suspicion to the point of therapeutic test, to say nothing of full investigation for syphilis* (provocative procedure etc)

The outstanding facts of this case are as follows

1 The patient, widow of fifty-three came with a chief complaint of stiff shoulder with pain in arms, neck, and legs.

2 The original medical diagnosis in her case was apparently "neuritis, first in one arm, then the second arm.

3 The preliminary medical history was apparently taken in such haste that the fact that her husband had died of tabes, and that while there had been no miscarriages there had been mortality of more than 75 per cent among her children in infancy was overlooked.

4 Radiogram of the wrist showed an old arthritis involving trapezoid and trapezium with destruction of articular surface

5 The wrist had begun to swell five months before was lanced three months later and was still open and draining, with the development of the lesion illustrated above without the index of suspicion rising to the point of having Wassermann test.

6. *The first Wassermann reaction taken the case was strongly positive*

7 The neurologic examination, cardiovascular examination, and spinal fluid were all negative

Suspect syphilis with every tumor especially if it develops slowly is indolent, and undergoes softening.

Redouble suspicion if after incision the lesion does not heal, but begins to extend with a serpiginous border. This is an excellent example of associated cutaneous and osseous lesions.

Vague pains, often diagnosed neuritis, are not uncommon feature of latent and late syphilis.

The family history is often better arouser of suspicion than is that of the individual patient, especially if she be woman.



Fig. 607

SYPHILITIC PSEUDO-TUBERCULOSIS AND THE WASSERMANN TEST

Male, aged thirty married, railroad brakeman.

A Cutaneous Lesion is Often the Best Guide to Syphilitic Process in th Bones or Joints. This patient came to the Clinic with chief complaint of loss of voice. H supposed that he had tuberculous laryngitis, and had been treated on this supposition by physician for tw and half months. H had been hoarse continuously for six months following severe cold. In the first three months of this period he had lost 30 pounds in weight.

In the collateral history it developed that he had been troubled with abscesses in the arms nd legs for four years, the right leg had been placed in cast for supposed tuberculous knee nd that the right elbow-joint had also become involved, ith several draining sinuses and good deal of scarring of the skin about the joint.

He Carried His Diagnosis on the Posterior Aspect of th Right Thigh. The classical group of sharply marginated punched-out ulcers along the dvancing edge of the process with superficial pigmented scar is diagnosis of syphilis on sight. Scarring on the front of the right knee is equally characteristic. The scars left by the draining sinuses are also pparent. While scarcely necessary for diagnosis it is interesting that the W ssermann reaction was repeatedly positive.

A most surprising therapeutic response followed six injections of arsphenamin. The patient regained his voice, the cutaneous lesions healed, nd year later movement had been so completely restored t all the affected joints that the patient was able to pass the draft examination for the army

Why Did This Patient Sustain Repeated Diagnoses of Tuberculosis in the Face of so Much Ground for Suspicion of Syphilis, to Say Nothing of Indubitable Evidence of Its Presence?

1. The fact that one sister had had tuberculosis was pparently partly responsible.
2. Few physicians realize that syphilis may produce bone and joint involvement with the formation of hat ppear to be tuberculous sinuses.
3. The index of suspicion in this patient medical attends ts was pparently low Certainly no one familiar ith the fundamental characteristics of lat cutaneous syphilids could have treated this patient for tuberculous osteo-arthritis and tuberculous laryngitis without Wassermann reaction. H had, moreover his tory of genital lesion twelve years before

The Index of Suspicion is What Makes the Diagnosis of Syphilis, Not Laboratory Tests.



Fig. 608.—This patient, aged fifty-one, illustrates the clue that may be furnished by a cutaneous scar adherent to bone in suspicious region (right clavicle) His chief complaint was backache of two months duration. Syphilitic backache has been emphasized in a publication by Klauder Roentgenographic study of the lumbar spine and stomach was negative. The stomach acids were low The blood Wassermann reaction was strongly positive. There was a scar of the ala nasi somewhat suggestive of syphilis. Immediate and complete relief of the backache followed treatment for the syphilitic infection.



Fig 609 —Importance of cutaneous lesion in diagnosis. This boy had bilaterally symmetrical hydrarthrosis of the knees which was referred t the syphilologist for an opinion as to the presence of stigmas of heredosyphilis, in which this picture may occur While there were no signs of syphilis, the eruption on the thorax quite positively identified the process as tuberculous. This is the grouped follicular eruption of lichen scrofulosorum tuberculid. The von Pirquet test w violently positive. Evidently tuberculous hydrarthrosis may closely simulate Clutton joints



Fig. 610.—This series illustrates (A) the nonunion of fracture in patient with syphilis who under treatment for the disease, without other measures, secured very rapid union (B) and functional restoration (C). The practice of taking blood Wassermann tests on ununited fractures led to the detection of this case, but syphilis as such need not be necessary cause of nonunion. The patient had been nurse, and on inquiry gave clear history of extragenital infection following the care of child ith pemphigoid syphilid, of whose infectiousness she had not been warned. In ununited fractures in which the blood Wassermann may present an equivocal result, roentgenograms of the entire bone or other bones may occasionally present periosteal lesions suggestive of syphilis.



Fig. 611.—Syphilitic pseudotuberculosis, with multiple sinuses and scrofulodermatous changes in the skin. The patient had been treated for four years as tuberculous, without Wassermann test. He presented pathognomonic cutaneous lesions of syphilis around other joint lesions. (See Fig. 607.)



Fig 612.

WILLIAMINOFF SYNDROME (?) BORDERLINE BETWEEN SYPHILIS AND TUBERCULOSIS, OR NON-SPECIFIC TREATMENT EFFECT AND HERXHEIMER REACTION IN GLANDULAR AND OSSEOUS TUBERCULOSIS (?)

A male, aged t enty-five.

Examined 1/17/1921.

Chief Complaint Swelling and redness of left knee. Old glands in the neck. Lumps on the back.

History Measles and lung trouble at age eight followed by enlarged cervical glands. Glands removed t operation, drained one year Numerous recurrences. Inflammation of the eyes age twelve. Running sores on neck age eight t t enty Good health age twenty-one to twenty-three. Mumps at age twenty-three followed by swelling of ankles, knees, and hands. Joints cleared up following injections for rheumatism. Back sprained two years ago, followed by pain in the legs. Thumb broken open following blow ith hammer Blood Wassermann reaction negative four months ago. *Diagnosis Congenital syphilis* based upon gummatous (?) swelling of the cheek and therapeutic response of neck lesions with local Herxheimer reactions to arsphenamin.

Examination Undersized male with Websterian dome, facies not suggestive. Extensive scarring of neck and face. Limitation of motion and sores over first t third lumbar vertebræ Metacarpophalangeal joint left thumb destroyed with false joint and sinuses. Left knee swollen, feverish, tender Afternoon temperature 100° F *x Ray*, multiple destructive arthritis of left thumb, right foot, spine and left knee. Hemoglobin, 65 per cent. *Blood Wassermann reaction negative* *Eye examination* Old interstitial keratitis with pigment deposits anterior surface right lens. No other osseous stigmas of heredosyphilis. *Special tuberculosis examination* chronic bronchitis, no evidence of tuberculosis in chest. *Sputum examination* negative Carbolfuchsin stains of pus from sinuses negative for tuberculosis.

Treatment Five neo-arsphenamin injections and 8 mercury salicylat injections ere given before coming t the clinic. Marked improvement took place in gummatous (?) lesions on face and neck. A Herxheimer reaction was observed. Further treatment, 6 injections neo-arsphenamin 0 3 t 0.5 gram, no mercury Progress was unfavorable. Treatment discontinued A tuberculous abscess in the left knee was drained, heliotherapy employed, and the patient improved.

Discussion

1. The suspicion of heredosyphilis rests entirely upon the patient general underdevelopment, his interstitial keratitis, and the initial improvement in the neck and face lesions under arsphenamin and mercury
2. Are these sufficient grounds for diagnosis of heredosyphilis? The process came on after measles and lung trouble. The patient ha never had positive blood Wassermann. The keratitis may have been tuberculous and the response to treatment non-specific. A Herxheimer reaction, moreover may occur in purely tuberculous lesions hen arsphenamin treatment is begun.
3. The possibility of syphilitic factor rests, therefore on rather slender basis. Everything which observed as contributing t diagnosis of heredosyphilis is almost equally applicable t diagnosis of complicating tuberculosis. The subsequent course of the case showed the tuberculous factor to be the more important. One must learn t distrust arsphenamin therapeutic tests.



FIG. 618.—THE CONFUSION OF SYPHILIS AND SARCOMA.

Left shoulder of woman who had sustained two surgical explorations with two diagnoses of sarcoma of the humerus. One of these diagnoses was given her in large diagnostic and teaching service, following examination of tissue. She was told her condition was inoperable, and radiotherapy advised, but refused. The report was confirmed by a second examination elsewhere. N blood Wassermann test seems to have been performed as part of either examination. When the blood Wassermann *test was finally taken it was strongly positive, and the* "sarcoma" vanished under treatment for syphilis. She has been under observation more than three years and is in excellent health.

The confusion of syphilis and sarcoma was much commoner and more distressing problem in pre-Wassermann days than it need be at the present time. Especially in heredosyphilis the appearance of painful swelling on long bone was the signal for surgical intervention. The obvious course nowadays is to take a routine blood Wassermann test as part of the medical examination to which all bone and joint cases should be subjected. The acceptance of a roentgenologic report without Wassermann test, or of biopsy report from tissue excised at exploration, especially from frozen section, without Wassermann test, opens the way for grave diagnostic error and neglects the most important single suspicion-arouser in the field of skeletal syphilis.

Fig. 614.

who has been und r my car as consultant for several
months We have cleaned up the disease in the mouth
twice but it recurs We have had an examin tion made
of the tissues and our pathologist reports n lignant
dis (round cel ed rcoma)
Th s peo le re in moderat circum tance but Are
nxi us to do wh tever they can for th boy nd I

THE CONFUSION OF SYPHILIS AND SARCOMA.

Photographic reproduction of part of letter accompanying patient to the clinic.

GUMMATA OF JAW AND PALATINE BONES. PATHOLOGIC DIAGNOSIS "ROUND-CELL SARCOMA. OPERATION WITH RECURRENCE. RECOVERY UNDER ANTISYPHILITIC TREATMENT

Boy aged ten.

4/20/16 Bone scraped for tumor of jaw
6/17/16 Dead bone and more scrapings removed.
Pathologist reports "Round-cell sarcoma.
9/23/16 Entered clinic. Tissue removed for diagnosis—no sarcoma found. Inflammatory tissue only
2/20/16 Two arsphenamin injections and treatment by mouth Improved.
3/19/17 Swelling lower end right humerus. Ray report Probably specific Mercury rubbed on locally
7/28/17 SWR ++++
7/30/17 7 injections arsphenamin 0 05 to 0.2 gm.
9/27/17 Improved. SWR +++
Mother SWR negative.
11/20/17 Nose and throat—large masses and crusts.
1/1/18 Interim on inunctions.
Much deformity perforation of palate, septum destroyed.
1/22/18 to 9/28/18 Seven injections arsphenamin 0 3 to 0 4 gm
SWR negative Process arrested

DISCUSSION

1 Syphilomas especially early before healing sets in, because of their high lymphocyte content, seem peculiarly susceptible to confusion with the pathologic picture of round-cell and lymphosarcoma. A Wassermann test and search for further evidence of syphilis will often prevent an error in diagnosis and needless operative interference.

2. Notice the inability of inunctions alone to hold the process in check (1/1/18).

Fig. 618.

CONFUSION OF EPITHELIOMA OF THE NASAL SEPTUM WITH POSTOPERATIVE SYPHILITIC OSTEITIS

A man, single, aged twenty-three years.

Examined 7/7/1919.

Complaint Repeated ttacks of swelling and inflammation in nasal side of left eye, with discharge of pus. Duration of symptoms, one year

History of Gonorrhea, 1918. No history of syphilis. Wassermann reaction negative.

Submucous Resection; intranasal dacryocystotomy

Good Results for Several Months.

Swelling and Crusting Within Nose. Foul discharge.

Blood Wassermann Reaction Negative Provocative negative. Marked destruction, nasal septum. Pieces of bone in discharge.

Diagnosis Syphilitic osteitis, nasal septum.

Returns After Six Arsphenamin Injections and 2 injections of mercury salicylate per week.

Hemorrhagic Nephritis (mercurial type), secondary to treatment (?). Small amount of albumin, many casts. Weight loss 40 pounds.

Wassermann Reaction Negative.

Rest in Bed. N improvement.

Secondary Antrum Infection Fever, further loss of weight.

N Response to Iodid or Arsphenamin.

Collapse of Nose.

Increased Edema of Face.

Septic Symptoms Nasal hemorrhage, steady decline in weight, increasing anemia, extreme fetor

Crusting and Ulceration appear at the ala nasi. Septum completely gone. Palat perforated.

Excision of Tissue from edge of alar ulcer

Diagnosis Epithelioma.

Intranasal Biopsy Squamous-cell epithelioma. Highly malignant.

Radium Intranasally Too late to vert fatal outcome

Discussion

1. In highly malignant syphilis of the osseous system the Wassermann reaction may be negative on the blood. On the other hand, persistent Wassermann negativity in rapidly progressive, destructive bone lesion should suggest error in diagnosis.
2. Syphilitic lesions hich progress in spit of combined treatment with arsphenamin, mercury and iodids should be searched for malignancy
3. The malignancy may be the primary condition, or secondary to the malignant degeneration of gumma. This is particularly likely to happen in lesions in the mouth, nose, and throat.
4. W were led astray in this case by the clinical picture and too ready an acceptance of the Wassermann negativity
5. While malignant syphilis undoubtedly exists, it seems probable that some of the reported cases may have been true malignant neoplasms instead of or in addition to syphilis.
6. An early biopsy should be made of tissue from the active margin inside the nose if the lesion resists treatment.
7. This case presented good general clinical picture of malignant syphilis, and was accepted as such on sight by several outside consultants.





Fig. 616.

HEMANGIO-ENDOTHELIOMA (ANGIOSARCOMA) SIMULATING LATE SYPHILIS OF THE SOFT TISSUES AND BONE. FALSE THERAPEUTIC TEST

A girl, aged fifteen.

Examined 10/27/16.

Chief Complaint. Deformity of the right wrist.

History. Broke right thumb at age of one year. Deformity of wrist appeared without symptoms at the age of twelve. Increasing weakness of the hand developed. Dislocation of wrist took place to the radial side with shortening and loss of movement, and slight crepitus. Radiogram showed cystic destruction of the lower end of the radius.

Treatment. Bone-graft done with good absorption and firm union. Blood Wassermann reaction at this time was negative. The patient returned three years later with skin broken down over the old operative wound. Numerous ulcers were appearing. She was then referred to the syphilologist. The lesion showed several draining sinuses, and considerable swelling, but nothing distinctive of syphilis. Provocative procedure was negative. *The lesion then healed completely under six injections of arsphenamine.* Another ulcer reappeared four months later. Biopsy which had been taken in 1918 was reported fibrous tissue, no osteoblasts. Biopsy taken from the relapsing ulcer was reported nonspecific chronic inflammatory tissue. Two more arsphenamine injections were given with immobilization, and gradual healing then took place. Patient returned home. Three years later patient again returned to the clinic. Ulceration was then much larger than at any previous time. Small subcutaneous nodules and dimpling of the skin near the scar and elbow were found. A clinical diagnosis of hemangio-endothelioma was now made. Pathologic diagnosis from a small fresh nodule was reported as hemangio-endothelioma. Amputation at the middle third of upper arm was performed. Radium treatment was applied to the lymph nodes.

DISCUSSION

This lesion definitely originated in bone if the history can be trusted. The clinical characteristics include onset in childhood or youth, antecedent trauma, a very prolonged course, late metastases, and a slow invasion of all tissues, with necrosis of bone and formation of hemorrhagic necrotic ulcers. The serpiginous outline often suggests syphilis.

Pathologic examination of tissue from old ulcers shows little except granulomatous changes, associated with secondary infection. The diagnosis must be made from fresh cutaneous nodules as discussed in connection with Fig. 871 and on p. 710.

The response of what is fundamentally a malignant process to arsphenamine seems remarkable but undoubtedly occurred on this occasion in this case. Some improvement was noted in Fig. 871.

Fig. 617

(See Fig. 96 for illustration.)

GUMMA OF THE RIBS ILLUSTRATING TRAUMATIC ONSET AND DELAYED HERXHEIMER EFFECT IN BONE LESIONS

A man, aged fifty-two.

Examined 4/10/21

Chief Complaint Pain in the right chest at the site of a bruise.

History Injured by being thrown against a window ledge ten months ago, striking ribs on right side of chest. Soreness began one week later but continued work for one month. *x*-Ray taken, opinion given as "broken cartilage." Second *x*-ray opinion "blood-clot." Laid off from work five weeks. Pain and tenderness continued on breathing and pressure. A diffuse swelling the size of a hand appeared two or three days after injury. Lumps began to appear, softened, were lanced and drained, and packed with gauze. Blood Wassermann reaction taken one week ago was strongly positive. History of penile lesion thirty-four years ago. Mixed treatment for one year.

Examination *Subcutaneous, doughy induration of right eleventh and twelfth ribs and* intercostal spaces in the posterior axillary line. Ulcer 1 cm. in diameter with greenish slough. *X*-Ray of chest and ribs negative. Blood Wassermann reaction negative, but three plus two days later. Blood, urine, eyes, ears, blood-pressure all normal.

Consultant's Opinion Gummatous osteomyelitis of eleventh and twelfth ribs with sinus formation.

Syphilologic Examination

Wassermann series three strong positive in seven tests.

Spinal fluid negative.

Treatment *Mercurial therapeutic test* of ten injections of mercury succinimid, with definite improvement, pain and induration subsiding. *Arsphenamin* 0.2 to 0.5 gram, 6 injections. Discharge much increased with second arsphenamin injection. New sinuses, more induration, and more discharge with third arsphenamin. No marked improvement with fourth arsphenamin. Much drainage. Surgical exploration showed no changes in the ribs, and a diffuse doughy inflammatory infiltration, with much pus. Gland inflammatory. Four months later on mercury and potassium iodid, the lesion had completely healed. Marked weight gain. Spinal fluid negative. Blood Wassermann reaction now negative. Cardiovascular examination negative.

Discussion

1. This is a typical traumatic history in osseous syphilis.
2. Note that the pain and swelling do not begin for some days after the injury. The differential diagnosis included tuberculosis, which is not uncommon in this location, and carcinoma.
3. The mercurial therapeutic test was employed to differentiate the process from tuberculosis, which might have responded to arsphenamin.
4. Bone gummas, as in this case, frequently give a prolonged severe Herxheimer reaction with a steady increase in the severity of symptoms over three to five weeks. This may deceive the observer in a therapeutic test.
5. The Herxheimer reaction in this case was so prolonged that the syphilologist himself distrusted the result and called for a surgical exploration.
6. The fluctuating blood Wassermann reaction still further aroused a suspicion of non-specificity.
7. Six weeks to three months may be necessary to establish syphilis as the cause in cases of this type.

CHAPTER XVII

THE GASTRO INTESTINAL TRACT IN SYPHILIS

As W J Mayo has remarked, 95 per cent of patients who complain of trouble with the stomach have nothing the matter with the stomach. So in syphilis, the term syphilis of the gastro-intestinal tract" covers less than 5 per cent of the symptoms from the gastro-intestinal tract for which syphilis is directly or indirectly responsible. For purposes of clinical discussion, the subject is here differentiated into gastro-intestinal symptoms in syphilis and actual syphilis of the gastro-intestinal tract.

The Literature.—Contemplation of the literature which, especially in recent years, has burgeoned forth into wealth of contributions, at once gives the impression that syphilis of the gastro-intestinal tract is an affair of everyday occurrence. It offers an excellent illustration of the remarkable literary incrustation which accumulates about medical rarities t the expense of the commonplace and, for everyday practice, at least, far more important conditions. Hartwell has estimated that the literature on gastric syphilis as such contains approximately 200 reported cases. The increasing interest in the subject and improved diagnosis is rapidly extending the field, and experienced observers such as Eusterman are now demanding that every gastric lesion not indubitably malignant which is associated with coincident syphilis shall have the benefit of therapeutic test before operative intervention is permitted. Unquestionably such course as this will, especially in the field of gastric ulcer materially enlarge the recognized share of syphilis in pathology of the gastro-intestinal tract. The larger part of the accumulated literature deals with late manifestations, for the gastro-intestinal symptoms accompanying functional derangement conceivably traceable to lesions of the nervous system especially are relatively little understood. The particularly important contributions of the past decade include Wile's summary of the subject, the publications of Eusterman and Carman of the Mayo Clinic, of LeWald, the summary of the Continental literature by Gigon in the Jadassohn Handbuch, which contains practically no reference to the important American contributions, the contributions of Bensaude in the French literature, and the papers of Bockus and Bank, O'Leary Hartwell and Eusterman. The series of 93 cases from the Mayo clinic reported by Eusterman is the largest single group extant. Special aspects, including the association of duodenal ulcer with syphilis and particularly tabes have been presented by Hunt and Lisa and by Gougerot. *Spirochaeta pallida* is said to have been identified in 6 cases of syphilitic ulcer by Warthin, one of which has been reported. McNee found the organism in tumor mass in the stomach. Singer (1933) Williams and Kimmelstiel (1940) Freedberg and Barron (1940) have demonstrated the presence of other types of spirochetes in the gastric mucosa and glands but Harris and Morgan succeeded in proving the presence of *Spirochaeta pallida* by animal inoculation and transfer Gorham, in discussion of Freedberg and Barron, stated that bismuth therapy intramuscularly gave satisfactory results in gastric ulcerative lesions not of syphilitic origin, so that it is evident that syphilis of the stomach has its nonspecific margin of error in diagnosis by therapeutic test. Williams and Kimmelstiel stress the extensive phlebitis observed histologically as of differential importance. The histopathology has been fully considered by certain of the authors mentioned. Roentgenological criteria have been particularly analyzed by LeWald, Carman, and Moore and Aurelius. The literature of intestinal syphilis has been reviewed by LaGuardia, and Gigon gives an excellent summary of established conceptions. The gastroscopy of syphilis of the stomach has been dealt with by Schindler (1937), Moutier (1935) and in the American literature by Carey and Ylvisaker (1936) and Patterson, Rouse and Bagwell (1942)

Gastro-intestinal Symptoms and Lesions Associated with Syphilis.—In Fig 618 we have listed as completely as possible from our own experience and the literature the various manifestations of syphilis involving or alleged to involve the gastro-intestinal tract. Except for the functional disturbances and

Fig. 616.

GASTRO-INTESTINAL SYMPTOMS AND LESIONS ASSOCIATED WITH SYPHILIS

1. Neurosyphilitic concomitants.
   (a) Functional disturbances disappearing on treatment associated with symptoms of "neurosis" and abnormal spinal fluid.
   (b) Syphilitic dyspepsia and bulimia.
   (c) Duodenal ulcer associated with tabes.
   (d) Coelialgia.
   (e) Tabetic crises.
2. Syphilitic parotitis.
3. Syphilitic oesophageal secondary lesions, gummatous infiltration, and stricture.
4. Syphilitic cardiospasm ("achalasia," Hurst, Bockus and Bank)
5. Gastric hypochlorhydria—60 per cent of young adults with syphilis (Neugebauer)
6. Gastritis, acute syphilitic—during secondary period, rare.
7. Gastritis, chronic catarrhal—vomiting, achlorhydria, hypermotility therapeutic test positive, secretory function sometimes restored (Wile, Bockus and Bank).
8. Syphilitic idiopathic gastric hemorrhage (varices?)
9. Syphilitic solitary gastric ulcer (cases observed by Warthin, Blackford, Eusterman, Stokes, Gougerot, Bockus and Bank)
10. Syphilitic multiple ulcers—the usual manifestation of gumma of the stomach.
11. Diffuse syphilitic fibrosis ("syphilitic linitis plastica")
12. Duodenal ulcer in syphilis (existence unestablished)
13. Syphilitic duodenitis (Alvarez in discussion, existence unsettled)
14. Syphilitic enteritis.
15. Syphilitic jejunal infiltration and ulcers (Warthin, personal communication, MacCallum, Gutman, LaGuardia) The commonest form of the excessively rare intestinal syphilis.
16. Syphilis of the sigmoid and rectum—anal chancre, proctitis, solitary gumma, infiltrated syphilid (gummatous proctitis and periproctitis with stricture) anorectal elephantiasic syphiloma of Fournier

neurosyphilitic concomitants presently to be described, all the remaining items belong essentially in the category of rarities, some of them still unproved. Syphilis of the small intestine is among the rarest known lesions of the disease.

GASTRIC SYMPTOMS AND FUNCTIONAL DISTURBANCES ASSOCIATED WITH SYPHILIS

The demonstration of the direct anatomicopathologic link between the symptoms or signs of gastro-intestinal disturbance and the syphilitic infection often lacks completeness, and may be confined to proof of the presence of syphilis in the patient and the disappearance of his symptoms under therapeutic test.

It is essential to recognize the pitfalls of this *post hoc* type of reasoning which is nowhere more striking than in the controversy over the existence of syphilitic duodenal ulcer. No one with any considerable experience in the treatment of syphilis has failed to see examples of the striking symptomatic response of duodenal ulcers in syphilitic patients subjected to treatment for syphilis without, however, the slightest structural change apparent in the lesion, so far as it is roentgenologically recognizable. This controversy extends itself into the field of syphilitic etiology in solitary gastric ulcer and to the diagnoses of syphilitic enteritis and syphilitic ulcerative disease of the colon, sigmoid, and rectum. In a similar way one may ascribe "functional" gastric derangements to syphilis of the nervous system, as revealed by an examination of the spinal fluid, and note the recovery of the patient coincident with the return of the fluid to normal. But it must be conceded that none of these chains of reasoning has the merit of absolute conclusiveness. One group of observers has therefore taken the stand that only through tissue examination, and if possible, the identification of *Spirochaeta pallida* can a diagnosis of structural syphilis of the gastro-intestinal tract be substantiated. From this perhaps ultraconservative viewpoint a consistent breaking-away is now apparent as diagnostic methods improve; and observers such as

Eusterman can, as we have already noted, feel justified in the stand that properly performed therapeutic test carries very great weight in the diagnosis of syphilis of the gastro-intestinal tract. In the effort to solve the problem, the presumptive character of the reasoning must first be recognized the demonstration of the concomitant syphilis must be as complete as possible; an organic lesion must be searched for with the utmost thoroughness; and when such lesion is found it must be closely observed during treatment and its disappearance noted, provided the method of examination is capable of showing healing as distinguished from scar. Where operative intervention is justified on general grounds, an effort must be made to secure tissue from lesions and to demonstrate the presence of *Spirochaeta pallida*, recalling, of course, the necessity for special fixation in neutral formalin of tissues to be used for this purpose. Singer has reported, however the presence in a gastric granuloma and in gastric carcinoma of what he regarded as nonsyphilitic spirochetes, in the latter instance in association with fusiform bacilli. Every precaution against *nonspecificity must be thrown around any therapeutic tests which are undertaken, and this* applies particularly to the indiscriminate use of the arsphenamines in inflammatory and ulcerative lesions of the upper and lower intestinal tract, a number of which are known to give a definite nonspecific response to the use of these arsenicals. Only one method of treatment should be used at a time and each should be given sufficiently long trial under observation to assure the negativity of the result, or the permanence of any improvement. Particularly in decisions involving the diffuse infiltrative syphilids with fibrosis in the stomach, prolongation of the therapeutic test in the absence of contraindications or danger to the patient from neglected operation for operable carcinoma, is essential.

Gastric Symptoms of Early Syphilis.—Wile estimates that, in one third of the early cases of syphilis which he has seen symptoms from the gastro-intestinal tract were part of the clinical picture the incidence in women being higher than in men In McFarland and Stokes s series of 230 early cases there were gastro-intestinal symptoms in 7 per cent.

The instrumentality of these symptoms in confusing the clinical picture of early syphilis with that of tuberculosis in patients, especially young women, in whom no florid exanthem may appear has been commented on (Chapter XII). Indirectly a variety of factors in early syphilis may be responsible for gastro-intestinal phase that fills the whole symptomatic horizon, as in basilar meningitis with eighth nerve and vestibular involvement in secondary syphilis. Early serious involvement of the liver is usually accompanied by gastric symptoms, especially gastric hemorrhage *Anorexia, epigastric distress, and so forth, are associated with severe febrile syphilis* as with any acute infection.

As a rule gastric complaints in cases of early syphilis are a minor element, seldom elicited without questioning, and readily responsive to effective systemic treatment for syphilis (Fig. 435)

The question of direct involvement of the gastric mucosa in early syphilis is largely speculative. Wile states that erosions and hemorrhagic areas have been found at necropsy but the occurrence of roseola of the mucous membranes of the stomach has not been determined, although the demonstration of eruptive lesions in the bladder with secondary syphilis of the skin makes it strongly probable that similar lesion may appear on other mucous-lined viscera.

Functional derangements of the stomach as detected by the test meal rest, however on the well-established basis of Neugebauer s study of 200 patients with florid exanthems, in whom a hypo-acidity was demonstrated in 62 per cent and hyperacidity in only 17 per cent. Luna has found subnormal secretory values in syphilitic patients Dorne and Tumpeer found hypochlorhydria in 91 per cent of prenatally syphilitic children between 4 and *15 years of age.* This functional change is thus demonstrable in a large proportion of patients with syphilis at all stages.

Neugebauer points out that the hypo-acidity may occur without gastric complaint. Whether the condition is due to changes in vagus tone or to an actual lesion of the mucosa, as various

authors suggest, is uncertain, but the high incidence of neurosyphilis among patients with syphilis without cutaneous manifestations, who complain of stomach trouble, leads us to support the neurogenic view

Gastric Symptoms of Latent and Late Syphilis.—Inasmuch as gastric complaints make up no small part of consultant medical practice, Stokes and Brown undertook an analysis from Mayo Clinic records, of the meaning of "stomach trouble" in persons with syphilis, based on a cross-section of 200 patients with syphilis seen in the Section on Dermatology and Syphilology in 1920 and 1921 who gave this as one of their complaints. Eighty-seven per cent of them gave stomach trouble as their *chief* symptom. The following is a summary of this study which is still a practical résumé of the diagnostic relations of the problem of functional gastric symptoms in syphilis

Summary and Discussion of Symptoms and Treatment.—Of 200 patients with syphilis who complained of gastric trouble, 75 per cent had neurosyphilis, 20 (10 per cent) had organic lesions (syphilitic or nonsyphilitic) of the gastro-intestinal tract, 9 (5 per cent) had lesions of the heart, and only 8 (4 per cent) had true syphilis of the stomach. The remaining 6 per cent had miscellaneous functional abnormalities.

The history of syphilitic infection is unreliable. Men give such a history three times as often as women. Sixty per cent of the men and 70 per cent of the women in this series did not give histories of secondaries. Only two thirds of those with histories of infection were given a diagnosis in the primary stage.

In only 36 per cent of the whole series of patients was syphilis recognized before they came to the clinic.

The medical diagnoses made before examination in the clinic were apparently largely based on histories (90 per cent) and blood Wassermann reactions (65 per cent) After examination in the clinic the diagnoses were based most often on histories (60 per cent) spinal fluid examinations (59 per cent) and blood Wassermann reactions (44 per cent)

Only 10 per cent of the patients had had spinal fluid examinations before entering the clinic, yet the findings were positive in 59 per cent. This test deserves greater popularity

Only 44 per cent of the patients gave positive Wassermann reactions on the blood when they entered the clinic 56 per cent gave negative reactions, largely as a result of treatment elsewhere. The greater diagnostic importance of the spinal fluid examination is obvious.

Seventy per cent of the patients with persistently negative Wassermann reactions on the blood not due to treatment had positive findings in the spinal fluid.

Neurosyphilis is not excluded as a cause of gastric complaints by negative blood Wassermann reactions and negative findings in the spinal fluid. Of 32 such patients, 40 per cent had gastric crises with neurological evidence of tabes dorsalis.

We suggest that the seat of the lesion in patients with gastric crises and negative spinal fluid findings is in the vagus, the abdominal ganglia, and the sympathetic system.

Fifty per cent of 122 patients had hypo-acidity· in 38 per cent the findings were normal. Hyperacidity was rare. The findings practically coincide with those of Neugebauer in early syphilis.

Eighty-four per cent of the roentgen-ray examinations of 132 patients were

negative, and only 16 per cent of the patients had definite or doubtful syphilitic lesions revealed by roentgenograms.

"Gastric neurosis" and "functional stomach" are dangerous diagnoses if any suggestion of syphilis is present. In 50 per cent of such cases blood Wassermann reactions were positive, and in more than 50 per cent the spinal fluid findings were positive.

Eighteen per cent of the patients with gastric trouble had had needless operations, 80 per cent of the latter before entering the clinic. In all but 2 of 35 patients there were clues to the underlying syphilis, which were not followed, or a negative blood Wassermann reaction that had been accepted as final when other evidence of syphilis could have been found.

One third of the needless laparotomies were on patients with gastric crises (see p. 1141).

The extraordinarily misleading influence of syphilis in the production of operable complexes to serve as pitfalls for the unwary surgeon is nowhere better illustrated than in the domain of "stomach trouble." Much of the discredit reflected on abdominal surgery by operations for gastric crises, and on functionally disturbed stomachs, associated with neurosyphilitic paresthesias simulating chronic conditions of the gall-bladder and appendix, pancreatitis, and so forth, is the result of a merely symptomatic approach. Too much emphasis is laid on the patient's story; hasty or snapshot examination and consultation are accepted, and a low index of suspicion for syphilis sends the patient for operation without a routine serologic test and the elementary checkup of pupils, reflexes, and sensory changes that should be an invariable preliminary to any decision to operate on the abdomen. The positive blood serologic reaction is too often overridden or ignored. The surgeon should not ignore positive evidence of the presence of syphilis from whatever source unless obvious emergency or the question of operable malignancy is really paramount. Therapeutic tests can give so prompt and definite a result in many cases of gastric complaints in which there is no need to rush the patient to the operating table that there is no reason for not employing them under proper guidance.

In 100 cases in which patients remained for treatment of syphilis the results were gratifying. Seventy per cent improved and 43 per cent were relieved of their complaint.

Treatment for syphilis underlying a gastric complaint must be directed according to the special indications in the case and must not be merely general. Different methods will be required for underlying syphilis of the nervous system, the stomach, or the heart, for example.

We observed striking symptomatic improvement in certain cases of gastric and duodenal ulcer in patients with neurosyphilis in whom the roentgen ray after treatment, revealed the lesion itself to be still present.

The spinal fluid examination stands out from this investigation as a procedure of the highest importance, outranking the serum serologic reaction in diagnostic syphilology as applied to internal medicine. In all suspicious gastric cases it should, with a neurological examination and full investigation for syphilis, be used before and not after diagnosis.

ORGANIC SYPHILIS OF THE GASTRO-INTESTINAL TRACT

Syphilis of the Salivary Glands.—Giron states that Veillet in 1913 collected the 41 cases in the literature, 30 of which were examples of parotitis, 7 involved the submaxillary glands

and 6 the sublingual glands. Congenital syphilis of the salivary glands is excessively rare but the *Spirochaeta pallida* has been demonstrated in one case. Neumann collected 5 examples of the acute parotitis of congenital syphilis. Gigon distinguished the condition from the syphilitic examples of Mikulicz syndrome which, in his opinion, is not invariably syphilitic. Pain, functional disturbance hard, indurated gummatous mass, and possible formation of salivary fistula are among the symptoms. Ankylosis of the jaw articulation may occur The therapeutic test is the chief diagnostic reliance.

Syphilis of th Esophagus.—Fournier observed this lesion four times in 5000 cases and Gaston collected 40 cases from the literature in 1906. In the beautiful example which Stokes had the opportunity to observe on Wile service, the process was evidently continuous with gummatous interstitial glossitis producing characteristic scarring of the tongue. Stokes has also observed 3 cases of stenosis apparently of syphilitic origin. The lesion presents nothing morphologically distinctive, though identification of gastric syphilid may assist in the diagnosis Esophagoscopy is responsible for the recognition of number of lesions of the esophagus, including some characteristic of the secondary stage of the disease, and this form of examination is stated by Gigon to be preferable to roentgenization. Gummatous cases are occasionally observed in conjunction with mediastinitis with the formation of fistulae, including tracheal fistula. Kampmeier and Jones (1941) reviewed the literature and reported 4 cases, with diaphragmatic involvement.

Acute Syphilitic Gastritis.—Syphilitic gastritis, usually regarded as one of the types of late syphilis of the stomach, is clinically so ill-defined that it is lost in the group of cases, already considered, of latent syphilis with gastric symptoms, but no roentgenologically demonstrable lesion of the stomach.

Eusterman states that, in association with gummatous syphilids of the stomach, pathologic changes of benign catarrhal gastritis are not uncommon. The clinical proof of the existence of the lesion must be its response to treatment, and when this is undertaken without adequate control, especially of the neurological factor It is difficult to determine just which of the gastric cases without organically demonstrable lesions should fall into the gastritis group.

Syphilitic Chronic Catarrhal Gastritis.—*This condition, considered by number of observers* as an early stage of diffuse gastric syphilis, is indistinguishable from gastritis associated with such conditions as chronic alcoholism or hepatic cirrhosis. It responds, often surprisingly to treatment and sometimes with partial or complete restoration of acid secretory function, even though absent to histamine test before treatment was begun (Bockus and Bank).

Gastric Hemorrhage in Syphilitics.—I general, syphilitic lesions of the stomach do not bleed readily the nature of the pathologic process with its obliterative endarteritic changes tending to prevent this. Sudden hemorrhage from the stomach is known, however, to occur in syphilitic patients without the presence of demonstrable lesion, though the presumption, of course, is alw ys in favor of varices associated with splenic or hepatic changes as the cause. Such sudden hemorrhages have been observed after treatment in patients without apparent stomach lesions (p. 408).

Late Syphilids of the Stomach.—Diffuse gummatous infiltration, nodulo-ulcerative lesions, with single or multiple ulcers, especially the latter essentially homologous with the nodulo-ulcerative late lesions of the skin and mucous membranes and often strikingly resembling them in configuration, are well recognized. Larger solitary gummas are also known to occur Diffuse syphilitic fibrosis such as one observes in parenchymatous organs, may also involve the stomach, giving rise to the clinical pictures confused with scirrhous carcinoma of the stomach and with "linitis plastica," whose syphilitic form was described by Singer In the tissues immediately surrounding the stomach, perigastritis with adhesions and inflammatory probably gummatous, lymphadenitis may occur

Syphilitic Solitary Gastric Ulcer—In the first edition of this work, Stokes somewhat timidly called attention to a group of 10 per cent of the Mayo Clinic cases in which clinician and roentgenologist united on the diagnosis of non syphilitic gastric ulcer Because it had become more or less routine in the *Mayo Clinic to subject patients with syphilis to treatment before operation,* he was able to prove these lesions to be syphilitic gastric ulcers by therapeutic

test before operation. The possibility of nonspecific effect was not at that time considered The process of opinion, while unanimity is by no means reached, has tended more and more to bring forward this possibility as one of practical importance in diagnosis. The earlier estimates of Ewald and Fenwick of 5 and 10 per cent as expressing the etiologic influence of syphilis in typical round

Fig 619

CLINICAL CHARACTERISTICS OF GASTRIC SYPHILIS

After Eusterman, Stokes, O'Leary Bockus and Bank

1 A rarity—69 cases in 25,000 syphilitic patients (O'Leary); 8 in 8000 cases of digestive tract disease (Moutier) More frequent as better understood. Largest series, Mayo Clinic, Eusterman 93 cases.
2. Men 70 per cent, women 30 per cent.
3. Age period thirty-six years in contrast to verage ulcer age of forty-five and cancer age of sixty-four years (Eusterman)
4 Averag duration of symptoms, two years.
5 Course progressive not intermittent, except t onset.
6 Four types: (1) epigastric pain or discomfort immediately after eating from the start made worse by solid food, 65 per cent, (2) pseudocancer group (15 per cent) gradual onset, mild, later pain, no food or alkali relief; (3) ulcer type (23 per cent) "pain-food-ease syndrome slightly atypical throughout course (4) no symptoms (history unreliable?).
7 Preservation of appetite or ravenous in contrast with cancer anorexia.
8. Patient not ill or emaciated i proportion to the extent of roentgenographic change or duration of clinical symptoms (Eusterman); (especially in diffuse syphilitic fibrosis, Bockus and Bank)
9 Achlorhydria, achylia (even to histamine) subacidity (Eusterman); normal or even high acid values in pyloric stenosis (primary retention) and gastrojejunal ulcers (Bockus and Bank)
10. Evidence of low gastric capacity (stomach inelastic) sense of fulness or bursting, ability t eat only small amounts, relief by vomiting.
11 Retention infrequent. Pylorus may be patulous and stomach empty rapidly (Eusterman, LeWald)
12. Hemorrhage uncommon (Eusterman) but absence not absolutely reliable differential point (Bockus and Bank)
13. Anemia mild, less frequent (10 per cent) e marked than in carcinoma.
14. Gastroscopic study reveals diffuse infiltrative nd ulcerative types of lesion ith fairly definit characteristics.
15 Doughy tender palpabl plastic infiltration rather than localized tumor suggestive. Presence or absence of tumor however not diagnostic (Stokes, Bockus and Bank).
16. Collateral evidence of syphilis symptoms and signs 27 per cent positive blood Wassermann reaction 92 100 per cent (Eusterman, Stokes, Bockus and Bank) spinal fluid Wassermann positive 11 per cent (O'Leary)
17 Therapeutic test rapidly and convincingly positiv in localized gummatous ulceration (improvement in t eeks) slower in diffuse infiltration (six weeks upward).
18. Essential features of positive test slow (sometimes spectacular) gain in weight, increase in food capacity decrease in anemia (O'Leary) Roentgenologic improvement may appear later

ulcer of the stomach have been regarded as an overestimate though Smithies has recently given 8 per cent as his personal impression of the proportion of round ulcers which are syphilitic in origin. Individual cases have been reported by Blackford, Eusterman and Bockus and Bank. Gougerot states that he has observed the condition repeatedly and Warthin is quoted as having found *Spirochaeta pallida* in 8 cases, one of them reported Bockus and Bank give

as important points favoring the diagnosis of syphilitic round ulcer the following

1 Failure of ordinary ulcer management.

2. The symptomatic relief marked weight gain and disappearance of anatomic defects following antisyphilitic treatment.

3 The presence of multiple roentgen-ray defects (*i. e* deformities other than and in addition to the gastric ulcer niche)

4 The lack of difference symptomatically from simple peptic ulcer except for a tendency toward greater weight loss.

5 The fact that gastric acidity is not necessarily altered.

Syphilitic Multiple Ulcer.—This, with diffuse syphilitic fibrosis, is the common picture of structural late syphilis of the stomach as comprised in the commonly used term "gastric syphilis." In Fig. 619 we have summarized from the literature the clinical characteristics emphasized in the larger reported series and in Fig 620 the roentgenological characteristics as worked out by Carman, LeWald, Moore and Aurelius, and Bockus and Bank, among other observers.

Fig. 620.

THE ROENTGENOLOGICAL CHARACTERISTICS OF GASTRIC SYPHILIS

After Carman, Moore and Aurelius, Bockus and Bank, LeWald, et al.

1. Filling defect of gastric outline, often but by no means always without corresponding palpable mass (presence not infrequent, LeWald)
2. Location, prepyloric 70 per cent; median or dumbbell (hourglass constriction) 22 per cent, diffuse 8 per cent.
3. Majority of lesions concentric or symmetrical (carcinoma eccentric)
4. Upper loculus may be tubular due to concentric extensive contraction.
5. Diminished gastric capacity with almost immediate evacuation of stomach (Carman, LeWald).
6. Six hour barium retention less common (15–40 per cent) than in carcinoma.
7 Lesion disproportionately extensive for ( ) general condition of patient (b) diagnosis of simple ulcer ( ) diagnosis of carcinoma.
8. Presence of multiple defects here symptoms are those of solitary gastric or of duodenal ulcer (Bockus and Bank)
9 Stiffening and lessened pliability of the gastric wall.
10. Absence of peristalsis from the involved area.
11. Compensatory dilatation of the esophagus in dumbbell types (Carman, LeWald)

W should like t this point to pay tribute to the remarkable and, in fact, unique cooperative work of Eusterman and Carman. The clinical observations of the former, and the roentgenologic acumen of the latter brought the diagnosis of gastric syphilis to an extraordinary level of accuracy and have made it seem essentially work of *supererogation to review the large* experience of the Mayo Clinic with gastric syphilis except by citation of their findings, methods and results. Stokes has, however ventured on summary of *25* cases in which the section on Dermatology and Syphilology had been called on to manage the actual treatment, or the therapeutic differential diagnosis, with view to orienting the problem from the syphilological standpoint.

It should be understood that multiple ulceration and diffuse gummatous infiltration of the wall of the stomach with cicatricial repair give rise to distortions of the gastric contour and to clinical symptoms which, in the main, are pathognomonic in their diagnostic value. As the experience of roentgenologists and clinicians with the condition increases, the accuracy of diagnosis and the positiveness of statements made in the literature as to the value of individual criteria steadily increase The critical issue for the patient is, of

course the differentiation of syphilis from cancer of the stomach. In order to examine this differential problem personally from the syphilological standpoint a cross section of 55 Mayo Clinic cases were reexamined with especial reference to diagnostic and differential considerations. This material still presents, in conjunction with Fig. 619 all of the essentials of the problem as we understand it today

DIAGNOSTIC AND DIFFERENTIAL CONSIDERATIONS BASED ON THE CROSS SECTION OF 55 CASES

The 55 patients who serve as the basis for the ensuing discussion of the diagnostic syphilology of gastric syphilids were referred to the Section on Dermatology and Syphilology either with diagnoses fully made by the cooperative work of the Eusterman and Carman groups in the clinic, or for therapeutic investigation when the diagnosis had reached an impasse. There are, however a few patients included in the series who were referred routinely because syphilis had been discovered in the examination, and others in whom surgical intervention had already been carried out with the finding of evidence which made further consideration of syphilis necessary The records were taken at random from the files. The opinions quoted are those of the gastroenterological consultants under Eusterman, the roentgenological consultants under Carman and

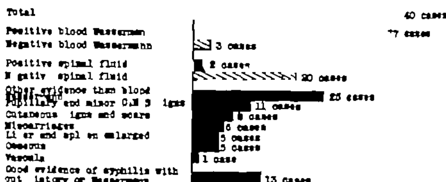


Fig. 621.—Collateral evidence of syphilis in 40 patients with gastric syphilids.

Moore, occasional surgical opinions, and the observations of the staff of the Section on Dermatology and Syphilology of the Mayo Clinic.

Of 55 patients studied, 40 had gastric syphilis, 13 carcinoma, 1 fibroma of the stomach, and 1 duodenal ulcer with false positive therapeutic test. No absolute sex predominance was apparent. Only 33 of 55 patients had had adequate histories taken with regard to venereal disease, a point on which improvement is possible. A high proportion of these 33 cases yielded positive histories of syphilis, a fact which always arouses some question as to whether the diagnosis is not being influenced too much by this rather untrustworthy criterion. It should be noted that in more than half of the 14 neoplastic cases there was likewise a history of syphilis, which explains most of the suspicion that led the patients to us. Forty of the 55 patients in the group proved, after the fullest possible study, to have gastric syphilis. The collateral evidence for syphilis in their histories is summarized in Fig. 621

The Wassermann Reaction.—The remarkable worth of the positive Wassermann reaction as a guide to gastric syphilis is certainly suggested by its presence in 37 of 40 cases. False positive blood Wassermann reactions in cases of cancer of the stomach are so unusual in our experience as to be of negligible importance. Eusterman and O'Leary have, however, both stressed the existence of seronegative cases. A single negative test cannot be trusted.

A conservative technic was used in most of these cases. The three negative reactions represent: (1) A case in which there were unmistakable residua of a severe rupial syphilid and scarring with bone destruction in the palate and pharynx; (2) a case in which the pathologic finding on tissue obtained at operation was a granuloma with vascular changes suggesting syphilis; and (3) a case of leather-bottle stomach in which, it must be admitted, little hope of establishing the diagnosis of syphilis existed, since the patient was a woman and the lesion not one which might be expected to respond to treatment.

The Spinal Fluid.—The remarkable immunity of the nervous system in cases of true visceral syphilis is substantiated by the very low proportion of cases in which the spinal fluid was abnormal—2 of 20 cases of gastric syphilis. O'Leary in a more recent survey found 11 Wassermann positive spinal fluids among 89 proved cases. The minor neurological signs did not appear to be the expression of an active neurosyphilis at the time of the gastric lesion.

Other Collateral Evidence of Syphilis.—The character and proportions of the general clinical evidence for syphilis are sufficiently indicated in Fig. 621

COMPARISON OF THE SYMPTOMATOLOGY OF GASTRIC SYPHILIS AND CARCINOMA (SYPHILIS PRESENT)

Figure 622 summarizes in percentages seven important points in the symptoms and findings of gastric syphilis, and compares them with those in cancer

1 Gastric Chemistry —Hydrochloric acid secretion is low in the overwhelming proportion of cases of gastric syphilid. Bockus and Bank, however believe that such a finding must be interpreted in terms of the type of syphilitic process under discussion and cannot be universally applied. There was no free hydrochloric acid in 82 per cent of the syphilitic stomachs in this series,

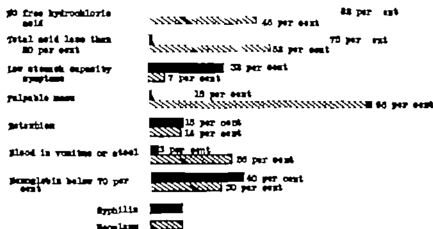


Fig. 622.—Résumé of findings in 54 patients with actual or suspected gastric syphilids.

as against 46 per cent of the small group of cases of cancer suspected of being syphilis. Total acidity is low in only a slightly smaller percentage. While the importance of subacidity is evident, normal and even high acids are not incompatible with a syphilitic gastric lesion A hyperacidity of free hydrochloric acid 84 combined 24 total 108, after six weeks of arsphenamine and mercury was reduced to free hydrochloric acid 20 combined 30 total acidity 50 Subacidity in the presence of a syphilitic lesion of the stomach likewise responds to treatment in some cases, an acidity of free hydrochloric 0 combined 20 total 20, increasing to free hydrochloric 20, total 50 and again to free hydrochloric 16, total 34

Achylia is evidently common and is more or less suggestive of syphilis of the stomach. Eusterman noted it in 80 per cent of the cases he studied

2. Gastric Capacity —This was interpreted in terms of symptoms suggestive of rigidity and loss of distensibility of the stomach (feeling of bursting with small amounts of food, ability to eat only small amounts without regurgitation or vomiting, and so forth) and appears, as Eusterman and Carman have both noted, in 26 per cent of cases of gastric syphilis.

3 Palpable Mass.—Emphasis is laid on this point in Eusterman's and Carman's differentiation of gastric syphilis and cancer on the basis of clinical findings. As Carman points out, the mass, if present, should correspond to the filling defect as seen with the fluoroscope and a filling defect with nothing palpable is strongly suggestive of syphilis. On the other hand, the criterion is not infallible and if too much relied on, may lead to error The present tendency in the literature is to give it less stress. One patient in this series with a palpable ridge was given a diagnosis of carcinoma 75 per cent, syphilis 25 per cent. There was complete symptomatic recovery under treatment, during more than four years of observation A second patient, with a palpable mass, diagnosed carcinoma, made a complete symptomatic recovery with marked objective improvement, as shown radiologically under treatment for his syphilis. A palpable ridge or mass is, of course easily possible anatomically in cases of solitary gumma of the wall of the stomach, and an impression of a mass may be given by infiltrations with perigastritis.

4 Retention.—Retention is commonly considered to be suggestive of carcinoma it occurs nevertheless in about 15 per cent of cases of gastric syphilis, as it appears in this cross section. The grade of obstruction was usually moderate, being severe in only 1 case.

5 Hemorrhage.—A history of hemorrhage, melena, and the presence of blood in vomitus, washings of the stomach, and in the stools, as detected by guaiac and benzidine tests, is definitely more distinctive of carcinoma than of syphilis. This is in accord with the general picture presented by the syphilitic ulcer in all parts of the body Obliteration, with anemic ulceration, not erosive invasion of vessels with hemorrhage, is the distinctive feature of the pathology of the syphilitic lesion.

6 Anemia.—This condition is often spoken of as more marked and of more rapid onset in carcinoma than in syphilis of the stomach. It is not the *lowness of the hemoglobin* which may be marked in syphilis, but the *lowness in proportion to duration of symptoms* that is significant of cancer

7 Loss of Weight.—Eusterman, Carman Bockus and Bank and others emphasize the significance of the good condition of the patient in proportion to the duration of the trouble, in swinging the diagnosis of a gastric lesion toward syphilis. Eusterman speaks of patients with gastric syphilis as thin, but not cachectic, which describes most cases. The loss of weight with gastric syphilis is, however pronounced, and the comments passed on the appearance of the patients in the records of our cross section suggest that caution must again be used in the application of this criterion A distinction seems to lie in the rate of weight loss which in our patients with gastric syphilis averaged 34 pounds in twenty four months or 1 4 pounds each month, and in those with carcinoma suspected of being syphilis, 24 pounds in ten months, or nearly twice the rate in syphilis. In spite of these differences, however there were some really astounding losses of weight and cachectic emaciations among the patients with gastric syphilis, some of them being positively cadaverous in appearance. Too much emphasis should not, therefore be placed by the inexperienced on this criterion in diagnosis.

Roentgenological and Clinical Opinion before Treatment.—To us the outstanding fact from the summarized consultant opinions is the high proportion of actual diagnoses made by the roentgenologist (55 per cent), usually without the aid of the clinical history and findings, and the high total accuracy of diagnosis by cooperative methods. Seventy five per cent of patients

were given correct diagnoses outright before they were sent to the syphilologist for treatment, and in only 17 per cent was carcinoma given the greater weight of probability when the condition proved to be syphilis. The advantage possessed by the clinician in his knowledge of the whole story was apparent (55 vs 75 per cent) likewise the greater tendency of the roentgenologist to diagnose carcinoma or be noncommittal (32 vs. 20 per cent) In view of the greater seriousness of carcinoma for the patient, this tendency is desirable rather than otherwise.

Gastroscopic Appearances.—These are usually recognizable earlier and persist longer than the roentgenographic findings. *Early syphilis* —F W Reynolds describes a superficial gastritis as occurring in early syphilis. This would be susceptible of gastroscopic study He mentions in addition the occurrence of an interstitial infiltration of the submucosa and muscularis with thickening of the wall and stenosis of the lumen—a form of precocious tertiarism *Late syphilis* —Moutier describes three types of late gastric syphilis: (1) the tumor form (gummatous) healing with scar formation (2) the ulcerative forms—single or multiple which lead to scarring and hourglass stomach. Schindler and Patterson, Rouse and Bagwell describe these ulcers as having a characteristic gastroscopic appearance—they are usually situated in the lower third of the stomach, have a smooth shallow yellow base, livid, purplish red serpiginous borders, comparable to the late mucous membrane manifestation *e g* in the mouth. The lack of the normal red color is due to the underlying obliterative vasculitis of syphilis. Howles (1943) has a series of color plates. (3) Generalized infiltrative gastritis which leads to linitis plastica.

Types 1 and 3 are the most difficult to differentiate gastroscopically from similar lesions of different etiology; they tend, however to show a prominence of superficial blood vessels on the borders of the lesions with a pale mucosa. There is a flattened thickened appearance of the rugae with flexibility of the stomach wall remaining In many instances the tendency to narrowing of the antrum in the diffuse fibrosis of gastric syphilis can be observed gastroscopically The lumen is difficult to distend by inflation. Complete resolution can be observed after effective antisyphilitic therapy

OTHER GASTRODUODENAL LESIONS

Associations of Duodenal Ulcer with Syphilis.—Many interesting problems await fuller study in the association of duodenal symptoms with syphilis. There seems no reason *a priori* why syphilis should necessarily exempt the duodenum. Alvarez (in discussion of Bockus and Bank s paper) calls attention *to the differences between the pyloric and the duodenal mucosa from the metabolic* standpoint, but states that he has had reason to suspect in young subjects the existence of such a condition as syphilitic duodenitis. Mortimer reviewing the literature brings out the accepted view in the literature that syphilis of the intestinal tract tends to concentrate at the jejunum and reports a case apparently of duodenal syphilitic infiltration with palpable mass, and a satisfactory therapeutic test. Eusterman, and we ourselves, have been obliged to maintain that we have never seen an authentic and unquestionable case of duodenal syphilis, and particularly of duodenal ulcer convincingly syphilitic in origin. Bockus and Bank in their discussion of primary retention associated with syphilis of the stomach, mention the similarity in symptomatology be-

tween duodenal ulcer and this group of syphilitic abnormalities in gastric syphilis. In their discussion of duodenal ulcer they observed 7 syphilitic patients with typical duodenal defects, 4 of whom sustained relief from antisyphilitic treatment. In the first edition of this work Stokes reported also having observed the often striking relief of symptoms (see Fig. 627) which syphilitic patients who are duodenal ulcer bearers sustain under treatment for syphilis. He was unable, however to be convinced that the effect was necessarily specific, though he mentioned the possibility of a response associated with improvement in syphilis of the nervous system in a definite group of duodenal ulcers in tabetics to be presently discussed. Bockus and Bank, while recognizing the very great difficulty of distinguishing between syphilis with intercurrent duodenal ulcer and duodenal ulcer due to syphilis, suggest as possible criteria for a syphilitic etiology in duodenal ulcer the following

1 Presence of other roentgen ray deformities in addition to the bulbar defect.

2. Association of achylia gastrica with duodenal ulcer This condition is so rare that it should at once attract suspicion. Two of their patients had achlorhydria.

3 A marked improvement in the duodenal ulcer defect after antisyphilitic treatment. They have had one such case. The occurrence of such a group of findings in a Negro with syphilis seems to them strong presumptive evidence in favor of the syphilitic nature of the process. We may say from our personal experience that the general effect of rest and of the tonic action of properly conducted antisyphilitic treatment may be striking, so far as the symptomatology of duodenal ulcer is concerned and that reliance must be placed almost entirely on objective criteria in judging of the validity of a therapeutic test. It is precisely at this point that the therapeutic tests that we have conducted in duodenal ulcer associated with syphilis have failed.

A type of association between syphilis and duodenal ulcer to which attention was called in the first edition of this work is that between gastric and duodenal ulcer and tabes dorsalis. Hunt and Lisa who have reported the most recent series of cases exhibiting this association, say that it is uncommon. Crohn in this country and Roux, Carnot, and Bruyere have interested themselves in the problem. Hunt and Lisa reached the conclusion that the association does not represent, as might be thought probable, a trophic type of ulcerative change in the gastric or duodenal mucosa associated with a neurosyphilis. On the other hand, the coincidence remains to be explained Camp, in discussion of Hunt and Lisa's paper had been impressed with the fact that hemorrhage occurring in what appears to be a gastric crisis might or might not be, and certainly was not necessarily an evidence of the concomitant presence of ulcer He described a case of fatal hemorrhage in a tabetic for which no clinical cause whatever could be found and stated that in his experience the vomiting of small or even larger amounts of bright blood was not necessarily a rarity in gastric crisis Oppenheim and Hunt and Lisa believe hemorrhage in gastric crises to be an exceptional occurrence

Udaondo, Casteigs and Gonalons have called attention to the occurrence of tabetiform gastric crises in the course of gastroduodenal ulcer These, according to their description, are painful attacks attributable to the ulcer but bearing a marked resemblance to the gastric crises of tabes dorsalis. The differential diagnosis requires, of course the elimination of tabes by thoroughgoing physical and serological examination, together with appropriate analysis of

the gastric and duodenal secretions and roentgenological study These authors consider the gastric crises of tabes a neuritic lesion of the general type of solar neuralgia.

It is apparent, then, that gastroduodenal ulcer symptomatology particularly with coincident syphilis of the nervous system, requires painstaking investigation of the individual case to distinguish the various possibilities involved.

Syphilitic Linitis Plastica.—O'Leary following Lyon s work in the study of 38 cases at the Mayo Clinic with 25 postoperative studies, has emphasized the undesirability of this term inasmuch as linitis plastica is, historically at least, a term first applied to the clinical picture of the small-cell carcinoma of the stomach wall with diffuse infiltration Gigon states that the term is very properly disappearing from the literature. In Lyon s series, only 1 case of leather-bottle stomach was demonstrably syphilitic in origin. The morphological homologue of true linitis plastica is produced by diffuse syphilitic gastric fibrosis, the sequel of diffuse gummatous infiltration. It produces a thick walled tube or funnel-like stomach, inelastic and relatively rigid with patent pylorus, only in occasional cases, however stenosed. Secondary dilatation of the esophagus may occur In the differentiation of syphilis from other causes of this gastric lesion therapeutic test is of comparatively little assistance, for the fibrous changes respond only to a slight degree, if at all, to even prolonged treatment for syphilis. Exploration and operative intervention are therefore usually the only resort. Even in cases in which improvement occurs following treatment, ultimate operation may be unavoidable. Gastrectomy in these cases, if the patient lives long enough is apt to lead to symptoms of pernicious anemia which, as in the case reported by Poole and Foster (with review of the literature) was successfully controlled by liver extract and desiccated hog stomach.

THE TREATMENT OF GASTRIC SYPHILIS

Technical Methods.—In no domain of syphilotherapy unless it be in tardive heredosyphilis, do greater therapeutic satisfactions await one than in the management of gastric syphilis. Fortunately the difficult combinations of a visceral lesion with involvement of the vascular and nervous systems are unusual in cases of gastric syphilis, so that the problem of treatment is usually greatly simplified Unless the process is extraordinarily chronic and involves the most extensive fibrotic transformations the results are often prompt and astonishing. O'Leary however in summarizing the therapeutic tests at the Mayo Clinic, points out that gradual, steady recovery especially with weight gain and rise in hemoglobin may be even more characteristic of the response of a gastric syphilis than the spectacular recoveries of patients with sharply localized lesions. It is practically never necessary to prepare a patient who has an uncomplicated gastric syphilis with heavy metal or iodide. Arsphenamine or if the patient is much reduced and weakened, neoarsphenamine, initial dose 0.2 to 0.3 Gm. often produces first of all an immediate cessation of pain After the second injection in which a normal dose by body weight may be used, the patient is often astonished at his ability to eat all but the most indigestible foods without distress. This change may even take place within the first week after he begins treatment. The usual arsphenamine course of 6 to 8 injections alternating with bismuth or with mercury by inunction is well tolerated by most patients, and the case should, from this point on, be managed as late benign syphilis, giving a minimum of 3 courses of ars

phenamine with interim and coincident heavy-metal therapy Mercury by mouth is undesirable, and there is no occasion to use iodides, especially at the beginning of treatment. Bockus and Bank found them both inferior to neoarsphenamine and bismuth Gains in weight and well-being are phenomenal, as will be shown, and objective improvement demonstrable with the roentgen ray is common (Fig 625) Roentgenographic changes are, however not necessarily parallel to clinical improvement, and the most striking clinical gains may be secured with little or no apparent change in the fluoroscopic picture.

Residual Damage Structural Recovery—Residual damage produced by a chronic syphilid of the stomach interferes with recovery in two ways by the mechanical obstruction produced, as by strategically situated lesions in pyloric stenosis and by fibrotic changes in the walls of the stomach with shrinkage and reduction to ultimate functional incapacity as in cases of syphilitic linitis plastica or leather bottle stomach. Here again, however clinical estimates made before treatment of the amount of improvement possible may err and patients with supposedly little prospect of improvement on account of fibrosis, may nevertheless achieve excellent results. A badly strictured, hourglass stomach in one patient may pass enough soft food and liquids to permit of marked gains, while in another practically no progress will be made until a dilation or gastro-enterostomy relieves the situation. Strictures of the stomach may in certain cases be effectively dilated with the bougie and thread, as, for example, in Fig 630 in which postmortem examination after influenza revealed a stricture still so small that a lead pencil would scarcely pass, although following dilation the patient had been able to take solid food including meat, for months. A small proportion of patients with gastric syphilis continue in spite of apparent structural recovery to be subject to slight inconvenience on eating the less digestible foods. Others, whose stomachs are markedly contracted may be obliged to eat small amounts frequently but will have no symptoms if this precaution is taken.

Functional Recovery Gastric Chemistry—A certain amount of functional as well as structural restoration occurs in the stomach after treatment, as is evidenced by return to approximately normal chemistry from low or even from high acid values. This probably accounts for the completeness of many symptomatic recoveries in patients who had exhibited marked disturbance of gastric chemistry in association with structural changes

Delayed Response—The immediacy of the good result of treatment in gastric syphilis has been spoken of as one of its most striking features. Occasionally however patients improve more gradually but none the less certainly and after from six months to a year or even more are restored to normal, *although at the outset the gain may not have been marked*. This retarded therapeutic response should not be too hastily construed within the first three weeks as a negative result (Fig. 632) in patients who are undergoing therapeutic tests for gastric syphilis in the face of signs suggesting *inoperable* carcinoma. (The problem of *operable* carcinoma is entirely different.)

Summary of Results.—The results obtained in the management of gastric syphilis are summarized in Fig. 623 It is apparent that ultimate symptomatic results are excellent in as high as 50 per cent, and good and excellent in as high as 75 per cent of the cases. Therapeutic results rated as good or excellent were obtained in 10 of 24 cases about 41 per cent, without any change in the radiogram. Practically complete recovery both clinically and roentgenologically was secured in 8 cases (30 per cent)

Weight Curve.—The weight curve of the patient under treatment for gastric syphilis presents some of the most remarkable examples of rapid gain to be found in the whole field of medical practice Part of the effect is to be attributed to the tonic action of the treatment, and not merely to a restoration of gastric function to normal for the total gain often exceeds by 10 to 15 per cent the greatest weight the patient had ever reached. In such cases there is usually a gradual decline to a point slightly above previous normal weight after treatment is stopped. Our best example is that of a patient with a loss of weight of 88 pounds extending over four years, who gained 83 pounds in six months 22.5 pounds the first three weeks, more than a pound a day· 42 pounds in forty-two days, 69 pounds in seventy days, and the balance of 16 pounds in the remaining one hundred and ten days.

All the patients with gastric syphilis in this series gained some weight under treatment. Fifteen ultimately gained more than 30 pounds each. The average weekly gain during the first course was, in most cases, from 1.5 to 2.5 pounds.

Fig. [illegible].

THERAPEUTIC RESULTS IN LATE GASTRIC SYPHILIS

	Results.					
	None.	Slight.	Fair	Good.	Excellent.	Total cases.
Immediate symptomatic improvement in gastric syphilis during the first course (six weeks)	0	6	7	11	5	29
Ultimate symptomatic improvement in gastric syphilis (one to three years of treatment)	0	3	5	11	19	38
Structural improvement shown by ray in gastric syphilis	10	0	4	4	6	24
Symptomatic improvement in cancer suspected of being gastric syphilis.	4	2	3	0	0	9

The blood serologic reaction proved to be resistant in 14 of 36 cases, was reversed to negative in 4 and in 18 treatment had not been carried far enough to permit classification. It is in line with our general experience to expect the blood serologic reaction to be difficult of reversal in cases of visceral syphilis even without complications in the cardiovascular and nervous systems. We have never in gastric cases made the reversal of the blood serologic reaction a major therapeutic aim if it remained positive after the third arsphenamine course, 300 inunctions, and iodide, provided it was the only remaining evidence of active disease.

THE THERAPEUTIC TEST IN SUSPECTED GASTRIC SYPHILIS AND CARCINOMA OF THE STOMACH

The decision to carry out a therapeutic test for syphilis in the presence of an organic gastric lesion, the skilful conduct of the procedure, and the correct interpretation of the result are often a life and death matter Not infrequently

it is the only means, short of surgical exploration, of establishing a diagnosis. It must at times be insisted on by the clinician against the advice of the surgeon On the other hand there are times when the operability of the patient would be lessened by the least delay or when operability itself is actually in question when the surgeon should make an exploration before treatment is undertaken. The following tabulation (Fig. 624) summarizes the cases in this series in which the therapeutic test was of critical importance

Fig. 624

	Cases.
SUSPECTED CARCINOMA PROVED TO BE SYPHILIS	
Clinically or roentgenologically diagnosed definitely as cancer but proved to be syphilis by therapeutic test	3
Clinically or roentgenologically diagnosed definitely as cancer explored, and found t be syphilis	4
Clinically or roentgenologically diagnosed probably cancer but proved to be syphilis by therapeutic test	3
SUSPECTED SYPHILIS PROVED TO BE CARCINOMA	
Clinically diagnosed probable syphilis, but proved to be neoplasm by negative therapeutic test and exploration	1
Clinically diagnosed possible syphilis, proved to be cancer by negative therapeutic test and outcome	5
Clinically diagnosed possible syphilis with apparently positive therapeutic test, proved at operation t be cancer	2
BENIGN SIMPLE ULCER PROVED TO BE SYPHILIS	
Clinically or roentgenologically diagnosed as peptic ulcer proved to be syphilis by therapeutic test (one recovery symptomatic, three both symptomatically and by -ray)	4

Nonspecificity Factor—The question of the specificity of a therapeutic test for syphilis in a patient who may have carcinoma or other form of infiltrative or especially ulcerative lesion in which Vincent or other spirochetosis may be a factor (Singer Gorham discussing Freedberg and Barron) is one of special importance It will be noted that in 2 of 7 cases in which this question was confronted a sufficiently marked improvement in a case of carcinoma was obtained to lead to the temporary diagnosis of syphilis, later reversed by the finding at operation when the patient finally began to decline again (Figs. 634 635) Moreover in Fig 624 it will be seen that slight and fair improvement was made in 5 patients with cancer The tonic effect of the arsphenamine, which it is essential to use if a rapid effect is to be obtained before operation, may evidently therefore give rise to confusing improvement in some cases, especially in slow-growing scirrhous carcinoma and in other types of cancer in patients who also have syphilis. In view of this element of uncertainty in the therapeutic test, when used for differentiating gastric syphilis and gastric cancer we have been led to advise the preoperative administration in operable cases of 2 injections of arsphenamine 0.3 Gm. each with a three-day interval. If improvement within seven days is not very pronounced and if the operability of the patient may be decreased by further delay an exploration should be performed Complete disappearance of most symptoms will often occur within from seven to ten days after this amount of treatment for a gastric syphilid In critical cases mere slight improvement should not be accepted as a positive therapeutic test

The Issue of Operability—The use of a therapeutic test to differentiate

syphilis from carcinoma of the stomach is, then, conditioned by the issue of operability of the possible cancer If the lesion is inoperable and syphilis present or presumptive, arsphenamine treatment should always be given and as Bockus and Bank emphasize, carried through an almost indefinite period. But clinical improvement does not clinch the diagnosis until enough time has



A



B



C

Fig. 623.—Roentgenograms of syphilis of the stomach, showing successively the condition before treatment, the improvement produced by six weeks of treatment for syphilis, and complete recovery with normal stomach outlines one year later (Case reported by Eusterman, Med. Clin. N Amer November 1919 p. 609)

elapsed for carcinoma to prove fatal or unless clinical relief is supported by roentgenological evidence of cure of the lesion. The weight curve is often helpful and a patient whose weight continues to drop under treatment, even though his symptoms are somewhat relieved, probably has carcinoma. Failure to relieve pain, although the patient may gain weight and appetite, is again in favor of cancer

Fig. 628.

PREOPERATIVE BLOOD WASSERMANN TEST IN GASTRIC DIAGNOSIS. PREOPERATIVE DIAGNOSIS OF ULCER WITH OBSTRUCTION FOUND TO BE MULTIPLE SYPHILITIC GASTRIC ULCERS

Male, aged thirty-seven, brakeman.

Chief Complaint Food distress after meals, duration nine months. Fulness nd heaviness in epigastrium.
Pain Not Relieved by Food or Soda. N colic. N nausea or vomiting. Takes milk only
Denies Syphilis Possible primary on lip eight years ago.
Examination Epigastric tenderness, no mass. Test-meal Free HCl 0, total 18. Food remnants.
x **Ray** **Lesion at Outlet.** Moderat retention.
N Blood Wassermann Test Taken.

Clinical Diagnosis: Gastric ulcer at pylorus with obstruction. Operation advised.
Operative Findings: Multiple Ulcers of the stomach.
Punctured with Cautery and specimen removed for diagnosis. Chronic appendicitis, slight pancreatitis.
Pathologic Report Very inflammatory ulcer
Surgeon Advises Further Examination for possibility of syphilis.
Postoperative Blood Wassermann: Repeatedly strong positive.
Treatment Begun.
Excellent Therapeuti Result.

DISCUSSION

1 Low acids in young man with ulcer might arouse suspicion of syphilis. In any event, routine preoperative Wassermann is never amiss.
2 Multiple gastric ulcers, also, should arouse suspicion of syphilis.
3 Judging merely from experience in the treatment of gastric syphilis, this type of operation, where possible, is much preferable to the extensive resections often considered necessary on exploration.
4. Inflammatory infiltratio found in such cases will often subside with excellent functional result under treatment for syphilis.

Fig 629

SYPHILITIC GASTRIC ULCER. OPERATION ADVISED HEALED BY TREATMENT

Woman, aged sixty-four married.

Chief Complaint Dull aching pain (t tacks) upper epigastrium and belching of gas, thirty years
Onset two t four hours after meals. Vomiting and soda relief
T years remission ended 1918.
Weight Loss 35 pounds in si months. Extensive itching eruption, wrists, palms, ankles, eighteen years
Examination Eruption as above. Slight arteriosclerosis. Systolic mitral murmur
Palpable Nodule in Abdomen, small, hard, tender below ensiform.
Blood and Urine Normal.

Blood Wassermann Reaction: Strong positive
Stomach Examination: Free HCl 12, total 20
Ray of Stomach fter belladonna.
Small Ulcer on Lesser Curvature.
Diagnosis: Gastric ulcer Mitral regurgitation, simple goiter latent or cutaneous syphilis.
Operation Advised Refused.
Treatment for Syphilis 6 injections arsphenamil 0 ⅓ t 0.6 gm.
Results: Complete Disappearance of All Gastric Symptoms.
-**Ray Report** Ulcer healed.

DISCUSSION

1 The entire complex apparently due t syphilis. The eruption vanished, there was marked eight gain, the W ssermann remained positive for time later negative.
2. There was no hange in gastric chemistry Low acids w th an ulcer in syphilis may justify therapeutic test before operation.
3. On account of patient age treatment w not pushed. She has been ell three years, with no recurrence of gastric symptoms.

Clinical Knowledge of Syphilitic Gastric Ulcer Can Be Extended by Less Operation and More Therapeutic Test in Pati nts with Combination of Syphilis and Ulcer

Fig. 630.

GASTRIC SYPHILID WITH EXTREME CACHEXIA AND AMAZING RESPONSE. DILATATION OF STRICTURED HOUR-GLASS WITH EXCELLENT RESULT

Male, aged thirty-seven, farmer

Chief Complaint: Vomiting, four years duration.
Penile Lesion: Fifteen years ago. Two courses injections at the time.
Examination *Extreme emaciation.* Height, 6 feet, 3 inches; weight, 100 pounds.
Pain and cramps constant.
Takes liquids only
Severe diarrhea.
Much reduced gastric capacity
No Palpable Mass. Free HCl 0, total 8.
Stomach x Ray Hour-glass, syphilitic type.
Almost Complete Obstruction shown by beefsteak meal.
Urine Many hyaline and granular casts, albumin.
Blood Wassermann Strong positive.
Treatment 4 injections neo-arsphenamin, 0.3 to 0.6 gm.
Amazing Transformation Gained 22½ pounds in twenty-one days. Nephritis disappeared. Still cannot eat solid food. Vomits immediately with pain.
Strictured Hour-glass Dilated to 30 F
After 7 Arsphenamin Injections
Weight gain 63 pounds. Urine normal. Eats everything but meat.
Blood Wassermann Persistently positive.
Patient Died of Influenza at the end of his second arsphenamin course after Complete Restoration to Physical Health. Total weight gain 85 pounds.
Autopsy Large stomach with lead-pencil sized stricture of pars media, 10 cm. long. Marked dilatation of cardia and lower esophagus, and of duodenum.

Discussion

1. An example of the treatment of gastric syphilids at its best.
2. Dilatation of the strictured hour-glass was an effective substitute for operative intervention. Resection of two-thirds of the stomach would have impaired the result. Function was excellent in spite of the marked deformity
3. The nephrosis was not unfavorably influenced by treatment.

Fig. 631

CLINICAL AND ROENTGENOLOGIC DIAGNOSIS, OPERABLE CARCINOMA OF THE STOMACH. SYPHILIS PRESENT. SYMPTOMATIC RECOVERY WITH THIRD ARSPHENAMIN INJECTION. SUBSEQUENT STRUCTURAL IMPROVEMENT

Male, aged thirty-two, nurse.

Examined 5/1/16.
Chief Complaint Stomach trouble. Penile sores. Scrotal ulceration, sores on lips ten years ago.
Duration of Stomach Symptoms T years. Stiffness in shoulders and neck. Gradual loss of weight. Dull gnawing epigastric pain began five years ago. Onset two or three hours p. c. Food relief Pain disappeared after two months. Very little since. One month later vomiting began. No solids seem to pass from stomach. Typical retention vomiting. Home doctor said ulcer at the pylorus with healing obstruction.
Examination Thin, slightly anemic. Weight loss 34 pounds. Scars of nodulo-ulcerative syphilid, scrotum, and lips. Hemoglobin 61 per cent. Test-meal Free HCl acid 0, combined HCl 70 total quantity 600 c.c. Food remnants present.
Roentgenologic Examination Operable carcinoma of the stomach, residue 3. Palpable ridge corresponding to filling defect.
Stool Examination: No parasites, no occult blood.
Blood Wassermann Reaction Strongly positive (2 tests) taken after x-ray examination.
Clinician's Diagnosis Pyloric carcinoma with obstruction 75 per cent., loss 25 per cent. Give salvarsan and send to hospital as soon as sterilized.
Treatment One week after first arsphenamin injection vomiting has disappeared. Diarrhea gone. Weight gain 6 pounds after third arsphenamin injection. All symptoms gone, eats everything Weight gained 10 pounds. After sixth arsphenamin injection no symptoms. X-Ray shows no change in stomach. Retention disappeared. Five months later, weight gained 47 pounds. No symptoms, gastric, x-ray unchanged. No retention. Eighteen months later condition excellent, gastric x-ray now shows improvement. Total period of observation two and one-half years.
Blood Wassermann Reaction Fixed positive Cardiovascular examination negative.

Fig. 632.

CLINICAL DIAGNOSIS, INOPERABLE CARCINOMA OF THE STOMACH. PALPABLE MASS. POSITIVE WASSERMANN. DELAYED THERAPEUTIC EFFECT LEADS TO EXPLORATION WITH CONFIRMATION OF DIAGNOSIS OF GASTRIC SYPHILIS. CLINICAL PICTURE OF SYPHILITIC LINITIS PLASTICA

Female, aged twenty-nine, single, stenographer

Examined 6/20/21.
Chief Complaint: Gastric distress.
Duration of Symptoms Nine months. Sharp cutting pain N relation to meals or food. Symptoms continuously progressive. Pains of late sharp and stabbing
Examination Thin girl, 23 pounds underweight. Physical examination: Tenderness epigastrium and right lower quadrant. Right kidney palpable. Movable mass in epigastrium on standing Hemoglobin 70 per cent. Test-meal: Free HCl acid 0, total acidity 12.
x Ray Diagnosis Inoperable carcinoma of the stomach. Advise W ssermann. Chest negative.
Blood Wassermann Reaction: Strongly positive.
Surgeon Opinion Short treatment for syphilis Explore unless response is immediate.
Treatment Three injection arsphenamin, 3 decigrams each.
N Definite Therapeutic Response Reconsideration of operability, exploration advised.
Operative Findings Slightly enlarged stomach general thickening of both walls to within 3 or 4 inches of the esophagus, obstruction near pylorus. N signs of metastasis. Spleen three times normal size, with perisplenitis and dhesion to the transverse mesocolon.
Diagnosis: Leather-bottle stomach, probably beginning syphilitic hour-glass contracture. Pathologic specimen Multiple small ulcers. Thickened fibrous walls. No malignancy Few giant-cells. A partial gastrectomy with posterior colic, end-to-side anastomosis.

DISCUSSION

With the multiple ulcers and pathologic picture in patient with syphilis there is practically no doubt that this is case of gastric syphilid with the diffuse inflammatory fibrotic changes of syphilitic linitis plastica.

The delayed therapeutic response is to be expected in cases in which there is very extensive fibrous change in the stomach. The change in surgical opinion regarding operability explains the exploration. The resection was necessitated by the probability that this stomach would ultimately have an obstructing degree of hour-glass contraction. No further treatment for syphilis was carried on in the clinic. The spinal fluid was negative. The fact that extensive gastric fibrosis will delay or minimize therapeutic effects must be borne in mind in interpreting therapeutic tests for syphilis on gastric lesions.

Fig. 633.

"INOPERABLE CARCINOMA AT THE CARDIA" PROVED TO BE SYPHILIS BY TREATMENT

Male, aged forty-three, married, laborer

Examined 9/14/17
Chief Complaint Gastric distress and vomiting
Duration of Symptoms: One and half years Began with gastric distress now vomits all food except milk and bread immediately after eating No tarry stools. No hematemesis.
Examination No palpable mass. Test-meal Free HCl 0, total acidity 10.
-Ray Inoperable carcinoma t the cardia. Hemoglobin 79 per cent.
Blood Wassermann Reaction Strongly positive.
Treatment Six arsphenamin injections, inunctions. Result All symptoms disappeared. All food except pork agrees. Weight gain 25 pounds. Period of observation four months.

DISCUSSION

Recalling the possibilities of error in the therapeutic test on carcinoma of the stomach associated with syphilis we cannot regard the diagnosis of gastric syphilid in this case as fully established without longer observation

Fig. 634.

THE FALSE THERAPEUTIC TEST FOR SYPHILIS IN GASTRIC CARCINOMA. ROENTGENOLOGIC DIAGNOSIS, GASTRIC SYPHILIS. MARKED IMPROVEMENT UNDER TREATMENT. DEATH FROM CARCINOMA

Male, aged forty-nine.

Chief Complaint: Carcinoma of Stomach, based on exploration one year before. Thickened, inflamed tissue. N definite growth found.

A Gland Had Been Removed and Diagnosed "Carcinoma.

Present Symptoms Five years duration, intermittent heavy feeling in epigastrium. Limited stomach capacity

Blood Wassermann Reaction Negative.

Provocative Procedure Negative

History of Chancroid twenty-five years ago.

Physical Findings Epigastrium slightly tender Mass adherent to scar Test meal Free HCl 8, total 18.

Ray of Stomach Luetic.

Spinal Fluid Negative.

Neurologic and Eye Examinations: Negative.

Therapeuti Test Elsewhere.

Given 9 injections of arsphenamin.

Gained 30 Pounds. Much General Improvement. Board-like Rigidity Relieved Can now eat moderately

Fatal Termination. Autopsy refused.

Discussion

1 Examination of the mesenteric gland t operation showed carcinoma in the opinion of competent laboratory

2. The case may combine both pictures, with secondary carcinomatous degeneration of gastric syphilid. This might explain the inflammatory changes t operation.

3. Be cautious in ruling out carcinoma by transient improvement obtained in therapeutic tests for syphilis in patients who present reasonable suspicion of carcinoma. Exploration is usually safer provided the lesion appears operable.

Fig. 635.

GASTRIC CARCINOMA IN A PATIENT WITH SYPHILIS. FALSE THERAPEUTIC TEST. IMPORTANCE OF REPEATED ROENTGENOLOGIC EXAMINATION AND OF HEMORRHAGE, OCCULT BLOOD, AND PERSISTENT ANEMIA

Male, aged forty-eight, single.

Chief Complaint Upper bdominal pain; food relief nocturnal exacerbation. Periodic, later continuous.

Hematemesis three months ago.

Soft Chancre eleven years go. Bubo twenty years ago.

Examination Marked Pallor Systolic blowing murmur t apex. Glands of axilla and upper arm. Abdominal tenderness both lower quadrants.

V *palpable mass or ridge.* Free HCl 0, total 8. Hgb. 45 per cent. Color index 0 6.

Blood present in Rehfuss meal. Guaiac negative, *benzidine positive*

Stomach Ray negative.

Blood Wassermann Reaction Strong positive.

Diagnosis Syphilis, probably visceral.

Treatment 2 arsphenamin injections.

Pain Not Relieved. Hemoglobin Dropping.

Transfusion. Arsphenamin continued.

Weight gain, 10 pounds. But pain persists.

Re-examination Six weeks interval. Now has palpable ridge.

Ray Now Shows Lesion of Body of Stomach. (Six weeks ago negative.)

Test-meal Free HCl 34 total 46.

Hemoglobin 55 per cent total eight gain 24 pounds.

Still Has Nocturnal Pain. Food and soda relief

Severe Gastric Hemorrhage t eeks after last arsphenamin injection.

Second Hemorrhage. Death Following Third Hemorrhage two weeks later

Autopsy: Carcinoma involving one-third of pyloric end of stomach, anterior surface. Metastasis to retroperitoneal nodes. Chronic valvular endocarditis.

Discussion

1. Improvement obscured the situation until mass and -ray findings developed.
2. Blood suggests carcinoma—hematemesis, occult blood, marked anemia.
3 Failure to relieve pain under treatment suggests carcinoma.
4. Improvement in gastric chemistry may follow treatment in syphilis.
5 The first negative -ray probably prevented possibly life-saving exploratory operation.

Fig. 636.

PERFORATING GASTRIC ULCER WASSERMANN STRONG POSITIVE. TREATED FOR SYPHILIS. CURE WITHOUT OPERATION

Male, aged forty-eight, divorced, farmer

Chief Complaint Dull pain in the stomach.

Duration of Symptoms: One year Gradually increasing weakness. Belching of gas. Distress after meals. Constant gnawing pain Regurgitation of food. No tarry stool.

History of Syphilis Chancre twenty years ago. Left-sided facial paralysis. Small amount of treatment by mouth.

Examination: Pupils irregular Slight general adenopathy Tenderness in the epigastrium. No mass felt.

Ray of the chest negative. Test meal Free HCl acid 10 to 22. Total acidity 20 to 42. Ray of the stomach Perforating gastric ulcer Grade 2 retention.

Blood Wassermann: Strongly positive.

Medical Opinion Perforating gastric ulcer Luetic history Positive Wassermann. Luetic ulcer (?) Atypical ulcer history Low acids. No intermissions; short duration.

Surgical Opinion Explore gastric ulcer May have preliminary treatment (antisyphilitic) but surgery should not be deferred too long

Treatment: Arsphenamin 0 3 gm. After this injection, gastric distress and other symptoms had practically disappeared. Arsphenamin 0 4 gm. The end of the second week of treatment patient had gained 15 pounds. Third week, 20 pounds. All symptoms disappeared. Re-ray of stomach after fourth arsphenamin injection showed small nitch on lesser curvature. Retention improved. One year later stomach negative. Test meal Free HCl acid 34, total acidity 48. Râles in the right per arouse suspicion of tuberculosis. Sputum examinations repeatedly negative. Blood Wassermann reaction fixed positive Spinal fluid negative.

DISCUSSION

The picking out of the high points of suspicion by the clinician permitted the syphilologist to make this successful therapeutic demonstration of syphilitic gastric ulcer in a patient who would otherwise roentgenologically have been typical surgical case, and in fact, in view of the perforating feature, an emergency case. The high points on which the differentiations were based were (1) history of syphilis, (2) positive Wassermann reaction, (3) short duration and continuous character of symptoms (no remissions), (4) low acids. It should be recalled, however, that some typical cases of gastric syphilis in our series had normal and in one instance high stomach acids.

Fig. 637

GASTRIC ULCER, NORMAL ACIDS. THOUGHT TO BE NON-SYPHILITIC. PROVED SYPHILITIC BY TREATMENT PREPARATORY TO OPERATION

Male, aged fifty-three married, farmer

Chief Complaint Five years of epigastric pain one-half t one hour p. c. Sour eructations. Much gas. Food and soda relief Typical periods of intermission as long as tw months. N change in character of symptoms. Made worse by pickles, sauerkraut, nd pples. Dyspepsia wakes him early in A. M. Exaggerated by hard work and worry No vomiting Very slight weight loss.

Examination Slight systolic murmur at the pex, otherwise negative. Hemoglobin 78. Test meal Free HCl 40 total cidity 52. Clinical diagnosis, duodenal or gastric ulcer

Ray Diagnosis Gastric ulcer Blood Wassermann reaction repeatedly strong positive.

Medical Consultant's Opinion History more of gastric tha of duodenal type. Do not think gastric ulcer is luetic. Advise operation and antispecific treatment.

Surgical Opinion Explore but gi antisyphilitic treatment first.

Tre tment Complet disappearance of all symptoms following 6 arsphenamin injections. Re-ray of stomach fter fifth arsphenamin injection Ulcer healed, completely negati

DISCUSSION

The caution of the surgeon in recommending antisyphilitic treatment before operating for gastric ulcer in patient with syphilis resulted in the cure of this ulcer without operation. N dietetic or other measures were employed. Note that the history is in practically every respect typical of that of gastric or duodenal ulcer and that the stomach acids were normal or above.

most careful treatment. Their condition presents a marked contrast to the rapid progress of the patients whose stomachs, with apparently an equally *extensive pathologic change*, have been allowed to recover under treatment for syphilis. This caution, of course, does not apply too literally to those cases of gastric syphilis in which exploration and operation must be performed to relieve severe symptoms of retention from pyloric stenosis and low hour-glass strictures. On the other hand, slight retention, especially in cases of syphilitic

Fig. 638.

RECURRENT GASTRIC HEMORRHAGE. *x*-RAY DIAGNOSIS DUODENAL ULCER. OPERATIVE FINDINGS, SPLENOMEGALY SPLENIC ADHESIONS TO STOMACH, MASSIVE GUMMATOUS HEPATITIS. NO GASTRIC OR DUODENAL LESION FOUND

Female, aged forty-two, housewife.

Chief Complaint: Six severe gastric hemorrhages in three years

Onset Five years ago. Gas and bloating of lower abdomen. Distress relieved by appendectomy Hemorrhages severe, prostrating Twice required transfusion. None for past year

Ray Diagnosis One year ago Ulcer near pylorus.

Examination: No thoracic or abdominal physical signs. T enty-three pounds over weight. Hemoglobin 60 per cent. Test-meal Free HCl acid 16, total acidity 50.

Ray of the Stomach (Three successive examination with belladonna) Final diagnosis Duodenal ulcer

Blood Wassermann Reaction: Repeatedly strongly positive. Spinal fluid examination negative.

Preoperative Antisyphilitic Treatment No distinctive response.

Clinical Diagnosis Bleeding duodenal ulcer

Operation: N ulcers found. Stomach very large Duodenum enlarged and thickened. Large gummatous mass in liver Spleen five times normal size. Adherent and pressing stomach in the middle. Splenectomy performed. Pathologic report: Diffuse chronic splenitis. Good recovery

DISCUSSION

In at least two instances I have seen the roentgenologic picture produced by splenic adhesions lead to report of duodenal ulcer

ulcer at the pylorus, is promptly and usually completely relieved by treatment, and should not be made the occasion for operative intervention until after at least one and perhaps two courses of treatment.

SYPHILIS OF THE INTESTINE AND COLON

Like other aspects of syphilis of the gastro-intestinal tract, syphilitic lesions of the small and large bowel are gradually being dragged from an obscurity which places them among the rarest manifestations of the disease. Fränkel, ith an experience of 19,000 necropsies, could identify only 3 cases. Gatewood and Kolodny identified 2 cases in 117,000 hospital patients. Goyena, Bianchi and Cachro (1936) found 6 cases in 810 cases of disease of the colon. The most complete study of late syphilitic lesions of the intestine in the recent literature is that of Nishikawa from the Anatomico-Pathologic Institute of the Rudolf Virchow Hospital in Berlin. This critical résumé of the literature, reinforced by 6 authenticated cases, the largest series ever collected, forms the basis for the following summary Riggs and De la Guardia have reported authenticated cases, citing Rieder and Gutmann criteria for diagnosis. Gigon summary in the Jadassohn Handbuch also gives an excellent résumé.

Clinically two forms of intestinal syphilis are described, the syphilitic enteritis present during the acute stage of the disease and resistant to all but medication for syphilis, and the late destructive and deforming local lesions, gummatous infiltrations of the intestinal walls, and syphilitic ulcers. The clinical study of diseases of the intestinal tract discloses so many conditions, such as endemic amebiasis, idiopathic chronic ulcerative colitis, for example, whose influence in intestinal pathology is not yet fully evaluated, that one is compelled t distrust the older statistical estimates and t accept with caution the etiologic significance of a mere coincidence of intestinal disease with systemic syphilis. The nonspecific effect of modern treatment for syphilis on enteritis of various types is not as yet understood, and the response of diarrhea to arsphenamine or even mercury may mean no more than an unrecognized intestinal parasitism, such as endamoeba or lamblia infection. Exceptional caution, therefore, must be exercised in attaching a diagnosis of syphilis to diarrheas occurring in the course of syphilitic infection, even though they respond to treatment. Particularly unreliable will be of course, the responses to arsphenamine therapy for arsphenamine is now well known as an effective intestinal antiparasitic, particularly in Lamblia and Amoeba infections. It is into these categories that some of our own cases, viewed at first as instances of intestinal syphilis, have resolved themselves. In the meanwhile it may be said that Wile at the time of publication of his monographic review of the subject had never seen an authentic case and from the large surgical material at the Mayo Clinic Stokes can recall only 2 cases which presented residua and concomitant circumstances suggestive of true syphilis of the intestines. Syphilitic appendicitis rather enthusiastically sponsored by Gaucher has never appeared in our experience, and only 2 cases by Trinkler have had histologic investigation.

The essential points in the clinical picture of late intestinal syphilis are well summarized by Nishikawa. The familiar dictum that syphilis of the intestines tends to affect the jejunum more than other portions of the tract is negated by Nishikawa findings, for lesions may occur at any point. Nishikawa ttaches major importance both from his own experience and the literature to the multiplicity of the lesions, the annular character of the infiltration which almost invariably forms localized constricting ring, and the hard, flat, nonulcerative plaques characteristic of the condition which differentiat it rather sharply from the tumor formations of carcinoma, the undermining lesions of tuberculosis, and the sharply marginated typhoid lesions with infiltrated borders. This preservation, practically intact, of the gummatous infiltrated plaques contrasts particularly with and is most important in the differentiation of the irregular broken-down lesions of carcinoma. Grouping and arrangement of lesions, suggested by some uthors as of differential importance, are shown by Gutmann, and Nishikawa to be without significance. The final criterion is the tendency to stenosis produced by the syphilitic lesions. Histologically the demonstration of *Spirochaeta pallida* is difficult, if not impossible. The characteristic histopathology of the process begins with the involvement of the vascular cone with tendency to segmental distribution of the lesions and to typical endarteritic pictures seen in section. The infiltration begins in the submucosa, and its character varies with the age and stage of the process, consisting t the start largely of small lymphocytes and plasma cells, with an increasing proportion of fibroblastic change in the older lesions. Sharply circumscribed gummatous nodules are recognized, and diffuse gummatous connective tissue form, akin to the diffuse infiltration of gastric syphilis.

T these criteria, applicable to the lesion when exposed t view would be inclined to add the following points.

1 The presence of syphilis should be demonstrated in the patient by collateral signs, particularly inasmuch as seronegative intestinal syphilis can be presumed to exist, especially in prenatal syphilitic patients.

2. The absence of parasitic infection should be demonstrated by repeated examinations.

3. Pancreatic function should be normal, in so far as this can be ascertained, for a supposed syphilitic diarrhea may be traceable, not to intestinal syphilis but t syphilitic pancreatitis.

4. There must be demonstrable absence of pulmonary oral or laryngeal tuberculosis and stool repeatedly negative for tuberculosis bacilli. Therapeutic tests should be conducted preferably with bismuth or mercury t reduce nonspecific effects to a minimum. The mercury should not be given by mouth and iodide may of course be used concurrently

5. Lymphogranuloma venereum must be eliminated by skin tests, history etc. The present tendency to include a form of ulcerative colitis among the lesions of the virus disease must be recalled.

Where the question of the differentiation of late intestinal syphilis with localized lues from carcinoma arises, we would be inclined to advocate exploratory confirmation of the diagnosis, unless the condition is inoperable—a view essentially in harmony with our experience with the same problem in gastric syphilis.

SYPHILIS OF THE RECTUM AND ANUS

The subject of syphilis of the rectum has been thrown into complete confusion by the rapid expansion of knowledge of lymphogranuloma venereum. Foreshadowed in the last edition the work of Frei, Grace and others has made it clear that most if not all of what has passed as syphilis, is in reality the newly identified virus infection in this region. It will probably require years, and the painstaking exclusion of lymphogranuloma venereum from each suspected case of syphilis before a new clinical picture of the anorectal syphiloma for example, can be built up. This will be made doubly difficult by doubts of the *specificity of the serologic tests for syphilis in lymphogranuloma venereum.* It is clear that present day differentiation of the anorectal manifestations of the two diseases resolves itself not into a differential morphology of lesions but a differentiation of the two diseases as such. The observer must of course familiarize himself with the clinical descriptions of lymphogranuloma venereum as contained in the basic monographs and papers (references given by Beerman, Ingraham and Stokes, Am. J Med Sc. 197 575 1939) These are briefly summarized on page 510 With the understanding that it will not tell the reader which disease he is looking at when confronted by the individual case, the following description from the second edition of this text is still adequate for what is known of syphilis of the rectum. It may be added that Buse has observed extensive leukoplakia of the rectum in a syphilitic

Syphilis of the sigmoid and rectum, like other types of syphilis of the intestinal tract, is conventionally described as early or late in its characteristics. The process associated with early syphilis is essentially proctitis with occasional papular infiltrations, thickening of the mucosa with hyperemia, and ulcerative processes. The onset is insidious, the symptoms essentially those of proctitis, including sense of heat and itching, and pain, blood, and pus with the evacuation. Unquestionably the frequency of these lesions is entangled with the problem of rectal gonorrhea and the traumatisms associated with sodomy Where syphilis is an etiologic factor, the response to treatment is said to be good and no stenosis occurs.

The later lesions of the rectum are usually described as conforming to one of three types, rectal gumma, rectal masses or tumors with their sequelae, and the anorectal syphiloma of Fournier All types are markedly more common in women than in men, although Bensaude, Masard, and Godard, in their large series found these conditions to be equally divided between the sexes. Zimmermann has called attention to the much greater frequency of rectal stricture and anorectal syphiloma in colored women.

Gummatous infiltration of the rectum is said to be extremely rare. Bensaude et al. described examples of anorectal gumma, proliferative proctitis, and rectal infiltrations simulating carcinoma. They describe type of rugous infiltration with multiple scattered superficial ulcerative lesions covered with whitish membrane in which marked nocturnal exacerbations of pain and diarrhea occurred with very prompt response to treatment for syphilis. Perirectal gummatous infiltration may lead to fistula formation and *even to rectovaginal fistula.*

The anorectal syphiloma of Fournier described below is the probable origin of such rectal strictures as can be ascribed to syphilis. The infiltration takes place about the ampulla, extending upward for 3 to 7 cm., and encircles the rectum, as in the case of upper intestinal infiltration. The chronic fibrous changes ensuing lead to high degree of stricture in the course of years.

Anorectal Syphiloma.—According to the observations of Koch and Jadassohn and of Bandler, this is an elephantiasic lesion of the perineum and vulva with secondary ulcerative manifestations resulting from lymphatic stasis secondary to chronic inflammatory changes in the inguinal lymph nodes. The earliest symptom is chronic obstipation. The conception of the exclusive or even principal etiologic influence of syphilis in this condition has been discounted by the studies of lymphogranuloma above mentioned.

Symptomatology of Rectal Syphilis.—The symptomatology associated with late syphilitic infiltrations of the rectum with stricture is, of course, quite nonspecific. Apart from the emphasis placed by certain observers on nocturnal exacerbation, the sense of heat and tension, tenesmus, pain with the bowel movement, gradually increasing obstipation, decrease in the caliber of the stool, plus mucus and blood, may be common to variety of granulomatous and even malignant conditions, as well as syphilis.

Gigon, while emphasizing the nonspecific character of the symptomatology and the wide range of clinical pictures on examination, states that the appearance of soft, easily bleeding vegetations in the rectum is suggestive of syphilis. The picture of rectal stricture he rates as much more characteristic. On palpation ringlike elevation of the mucous membrane is detectable or the cruciate stricture form may be recognized. With the proctoscope funnel-shaped narrowing 3 or 4 cm. deep is recognizable covered by a whitish, nonulcerated mucosa. Flat condylomas may be recognizable. Biopsy is often possible, but *Spirochaeta pallida* has thus far never been identified.

Mistaken Impressions of Frequency.—Structure of the rectum has as we have indicated been more or less traditionally accepted as of syphilitic origin in a high proportion of cases. In fact, if one is to accept the opinions of number of uthors, rectal syphilids are almost as common as syphilids of other parts of the intestine are rare. Individual experience in the matter may vary under unknown conditions. For example Bensaude, Mezard and Godard in 1930 published statistics on 226 rectal strictures observed since 1910, in which they found syphilis to be indubitably present in 61 per cent of the patients. From what we have seen of the difficulty of connecting syphilis with a rectal stricture by an unbroken chain of diagnostic or therapeutic reasoning, we are convinced that mere demonstration of concomitant syphilis is insufficient to prove the syphilitic origin of rectal lesion. As in syphilis of the colon, parasitism, nonspecific ulcerative colitis and proctitis, other infections and trauma or inflammatory changes secondary to treatment for hemorrhoids, all serve as confusing elements. Sodomy seems to have been a factor in some of the Continental series. Buie has summarized the experience of the Mayo Clinic with the problem of benign stricture of the rectum due to syphilis in terms which accord more closely with our personal impressions.

In reviewing 258 cases of rectal stricture seen in the Mayo Clinic from *1918 to 1922 Buie* found 55 patients who had had syphilis. During six years of this period syphilitic cases were reviewed by the syphilologist and treatment carried out in most cases, with signally disappointing results.

In dealing with rectal stricture one is, then, studying consequence and not cause, and while ill-advised operative interference, irritants, or medication may lead to picture not distinctive of syphilis, the obscure beginnings may nevertheless have been syphilitic in character Moreover treatment for syphilis applied late as a therapeutic test can be expected to have only limited value because of the functional disability entailed by the scarring produced by the healing processes. But in spite of these modifying considerations we have found clearly demonstrable syphilis of the rectum to be comparatively rare and the demonstration of syphilis as the cause usually weakened or set aside outright by the pronounced nonspecific effects of modern treatment for syphilis on the intestinal tract. Certainly we are not able to concede validity to the "feel" of stricture or t its location *ipso facto* as proof of its syphilitic origin.

Exclusion of Other Causes Before Treatment.—When syphilis is demonstrable on collateral evidence in patient who complains of rectal symptoms, with blood or pus in the stool, or who has ribbon or lead-pencil evacuation ven with comparatively few symptoms, an effort must be made t exclude other causes of stricture before treatment for syphilis is begun. Unless this precaution is taken the effect of course of arsphenamine in concealing the existence of an endameba infection may leave the issue of syphilitic infection in the patient permanently in doubt, to say nothing of its influence as factor in the rectal condition. The striking improvement both in local symptoms and general well-being in these patients may cause one completely to lose sight of other possibilities in the case All patients with an ulcerative process in the rectum should have roentgenological examinations of the colon for the detection of the characteristic changes of nonspecific ulcerative colitis, contraction and obliteration of the normal haustrations, with the final reduction of the bowel t a contracted, straight-walled tube Treatment for syphilis in cases of nonspecific ulcerative colitis is occasionally accompanied by temporary benefit which may give the impression of a positive therapeutic test. The all-important diagnostic tests for lymphogranuloma venereum are described on page 813. Paulson has described "bowel antigen" for skin tests in these cases, claiming greater sensitivity and specificity The use of sulfonamides and antimony in therapeutic test differentiation is not trust orthy

Operative Measures After Treatment.—While relief from pain and disappearance of ulceration may follow treatment for syphilis, operative measures, ranging from dilation under anesthesia to colostomy may be necessary to deal with the obstruction produced in cases of marked severity or long duration, and to prevent the recurrence of ulceration above the stricture due to mechanical interference with the passage of the stool and consequent continuous cycle of trauma and infection. Buie, in summarizing the experience of the Mayo Clinic on this point, rated the effects of dilation under anesthesia as temporary resection of the rectum as desirable but technically difficult, and colostomy and ileostomy as the most dependable form of treatment in severe

Fig. 630

GUMMA OF THE RECTUM WITH STRICTURE. TIBIAL PERIOSTITIS. NO SEROLOGIC EVIDENCE OF SYPHILIS. CURE OF PERIOSTITIS AND STRICTURE BY ANTISYPHILITIC TREATMENT (POSITIVE THERAPEUTIC TEST.)

Female, aged forty-nine, married.

Chief Complaint Rectal trouble. History 5 or 6 miscarriages. One child died three days old.

Onset Rectal Trouble ten years ago.

Operation Much relief Little control of rectal sphincter since. Pain and blood-streaked ribbon stools. Began again three months ago. Stool will not pass unless loose.

Examination Palpable lower cervical glands. Apparently tuberculous. Twenty years standing. Hemoglobin 45 per cent. R B.C. 3,300,000. Leukocytes 11,800

Proctoscopic Examination Scarring begins at anal canal, extends upward 10 cm. Stricture not over 1 cm. in diameter Ulcerated and bleeding. Anal sphincter incontinent. Posterior vaginal wall bulged forward by infiltrate between vagina and rectum. Impossible to reach cervix. Mass soft and boggy

Syphilologic Examination Provocative procedure negative. Spinal fluid examination negative. Osteomyelitis lower end left tibia. Some years duration. Tuberculosis diagnosed by J. B. Murphy 1910. Pupillary reflexes sluggish.

Neurologic Examination Residue of old typhoid myelitis. Residue and history of hemiplegia and aphasia two years before typhoid, possibly syphilitic. Stool examination negative.

Therapeutic Test 7 injections arsphenamin 3 to 4 decigrams. Bone lesion typical Herxheimer reaction, followed by complete recovery

Rectal Lesion Rapid Therapeutic Response 90 Per Cent. Improvement. Ulceration practically healed. Stricture no longer seriously obstructs. Period of observation one year

Blood Wassermann Reaction Never Positive. Spinal fluid examination negative. Symptoms of chronic bronchitis. Relieved by change of climate. No recurrence of rectal symptoms. Dilatation not necessary

DISCUSSION

Evidence for syphilis consists of suspicious history possible syphilitic hemiplegia and aphasia. Tibial periostitis and osteomyelitis with Herxheimer reaction under treatment followed by cure. Disappearance of ulceration and infiltration under arsphenamin and mercury N relapse during one year The continuously negative serology in this patient inevitably arouses the suspicion of non-specific therapeutic effect on low-grade tuberculosis. This is reinforced by the history of tuberculosis with glands of twenty years duration. On the whole however the evidence for syphilis much outweighs that for tuberculosis.

Note that the stricture is of the typical funicular type. For some of the possibilities of non-specific therapeutic effects on supposed syphilis of the rectum and intestine see above. Note also that as is commonly the case in syphilis of the rectum, no symptoms developed to attract the patient attention until stricture had developed.

cases. I colostomy cases through-and-through irrigation and local medication by proctoscope are invaluable. W have been much impressed with the comfort which these unfortunate, severely obstructed patients obtain from colostomy and their satisfaction with the operative result. Control of the diet to avoid flatulence and certain regularity of evacuation seem to be obtainable, and to do away with many of the theoretic objections to the procedure.

T all intents and purposes, then, the differentiation of the enteritis and enterocolitis of syphilis from other types of intestinal lesions depends on the elimination of tuberculosis, parasitism, and chronic ulcerative colitis and the differentiation of late lesions (gumma, and so forth) involves the elimination of carcinoma, tuberculosis, and actinomycosis, which, in practically all cases at outset, will require operative exploration for the good of the patient. The possibility of confusing actinomycosis of the cecum with syphilis on account of the occasional marked response of actinomycosis to arsphenamine and, of course, to the iodides may need to be recalled. Any pus obtained in the course of investigation or exploration should be promptly searched for sulphur bodies. The fallibility of arsenical therapeutic tests in all aspects of intestinal lesions must be constantly borne in mind.

Anal syphilids are considered in conjunction with cutaneous landmarks, Chapters XI and XII.

CHAPTER XVIII

SYPHILIS OF THE LIVER AND SPLEEN

Syphilis of the liver and spleen should be common. Both structures have enormous capillary sieves which strain out and dispose of large amounts of toxic and infectious circulating material with a minimum of symptomatic protest. As in the nervous system, so also in the liver and spleen, there is probably a high incidence of early reaction, taking the form of congestion with enlargement of the organ, and followed by recovery as the spirochetemia subsides. Only a relatively small proportion of patients who, at the onset, have a visceral reaction, will have symptoms directing attention to it, and a much smaller proportion will be likely to develop chronic reactions or late manifestations. The lowly estate of syphilis of the liver from the standpoint of clinical recognition, is well represented by McCrae's finding of only 56 cases (0.2 per cent) in 27 000 medical examinations, as contrasted with an incidence of 1.5 per cent in 3300 postmortems. Thus 1 case in 7 of syphilis of the liver was recognized clinically in the pre-Wassermann days, to which McCrae's figures are largely referable. Figure 642 presents our observations on the simple physical criterion of enlargement of liver or spleen in 419 patients with various forms of syphilis including preponderantly latent and late phases of the disease but excluding hepatosplenic syphilis as such. This checks fairly well against current estimates of the prevalence of syphilis (10 to 15 per cent) for if 1.5 per cent of necropsies in general disclose syphilis of the liver and if 10 per cent, clinically of those persons who have syphilis, have involvement of the liver there should be an incidence of all forms of syphilis approximating 15 per cent in all persons who come to necropsy. Hahn (1943) has recently reviewed the problem of hepatic syphilis.

A close association exists clinically between pathologic changes in the liver and spleen. As Rolleston says, the presence of an enlarged spleen with an upper abdominal mass should suggest cirrhosis. The widest range of combinations appears in any considerable group of syphilitic livers and spleens, from enormous livers with almost normal spleens, to extraordinary splenomegaly with no abnormalities detectable in the liver. It is experience with this range and variability which leads the clinical syphilologist to look with suspicion on such pictures as Banti's disease and even to insist that there are no features of splenic anemia which syphilis cannot reproduce. It is apparent, however from any considerable study that syphilis of the liver is much more common, or at least is much more commonly recognizable, than is syphilis of the spleen. Part of the reason lies in the silent character of the spleen, and in the fact that it must become considerably enlarged before it is detected as abnormal on physical examination. The liver on the other hand is more accessible to physical examination and operative inspection and being equipped with more ways of expressing pathologic change in symptoms through the biliary and portal mechanism more frequently forces itself on clinical attention.

Syphilis of the liver may be discussed clinically at the present time under the following heads (1) early acute benign hepatitis (2) syphilitic destructive hepatitis or acute yellow atrophy (3) subthreshold hepatic syphilis detected

by functional tests (4) hepatorecurrence (5) mild chronic hepatitis of latency; (6) diffuse and localized gummatous hepatitis (7) chronic interstitial pericellular cirrhosis of heredosyphilis (Chapter XXI) and (8) perihepatitis. The following summary will prepare for the discussion of the diagnosis as illustrated by our own material

Early Acute Benign Hepatitis.—This is rare complication of the florid eruptive stage of syphilis, first described by Gubler in 1853. Estimates of its frequency in syphilis range from 0.37 per cent (Werner) to 3 per cent (Reimer) Wile rates the incidence below 1 per cent. Stokes saw only one undoubted case in survey of 800 patients with early syphilis. Waugh (1937) saw four cases in 4,890 cases of early syphilis (0.08 per cent). The chief symptom is jaundice, the chief sign enlargement of the liver Weight loss to the point of emaciation may occur The condition is distinguished with difficulty from intercurrent catarrhal jaundice of nonspecific origin and from hepatorecurrence, and, in fact, the differentiation must rest entirely on: (1) The presence of chancre or secondary syphilitic eruption (usually roseola) (2) Herxheimer flare-up if treatment is begun with arsphenamine and (3) prompt cure as treatment is continued. Two to five weeks should complete the recovery of patient with early hepatitis, except for residual enlargement of the liver which may persist for some time, indicating that there is possibly diffuse inflammatory factor and proliferative element in the pathology A roseola of the bile ducts, condylomas of the ampulla, and pressure from enlarged nodes in the portal fissure are among the hypotheses as to etiologic mechanism. Reimer demonstrated the influence of local adenopathy as cause of obstructive pressure in 3 cases.

Elliott and Todd have reported particularly interesting case in which the hepatitis followed two months after the appearance of the primary lesion, and the functional injury to the liver could be followed by the icterus index together with the flare-up (Herxheimer effect) on the institution of bismuth treatment. Successive readings beginning with the first examination were 65, 116 (after first Bi injection), 214 (after second Bi injection) 62 (nine days later), 24, 13.6 (three weeks after treatment begun), 8 (fifth week). This was an effective demonstration both of therapeutic flare-up, the ability of bismuth to induce it, and proof of the syphilitic nature of the hepatitis by therapeutic test. Waugh saw no clinical signs of Herxheimer reaction in his four cases, treated, one with bismuth and three with an arsenical.

Syphilitic Destructive Hepatitis or Acute Yellow Atrophy (Icterus Gravis).—Among the various causes of fulminating destruction of the liver syphilis takes an undoubted, though rarely occupied, place. The complication is so rare that no one has been able to record personal experience of more than 3 cases (Richter); most syphilologists, including ourselves, can record one each. As conventionally described, the complication is an associate of the early period of the syphilitic infection, at times even preceding the secondary eruption (Michael) as in the case of acute syphilitic nephritis. It is sometimes seen in association with the mild or benign form of icterus, coming on without warning in cases apparently running an uneventful course. The incidence of 10 per cent grave icterus in cases of mild early syphilitic hepatitis indicates the rarity of the complication. As factor in acute yellow atrophy in general the instrumentality of syphilis may be inferred from Lebert figures in 1854, in which 7 of 72 patients had syphilis. Umber in 1911 brought the total of reported cases of grave icterus in the literature ascribed to syphilis to 50.

The investigations of Buschke and Zeroik in 1911 seem to have established grave icterus to the satisfaction of most observers, as syphilotoxic parenchymatous destructive hepatitis, with jaundice of nonobstructive type. According to Bursecinski, Fischer Bendig, and others no spirochetes are found in the liver O'Leary however states that Warthin has found the organisms in large numbers, and believes the process represents spirochetal crisis such as has been observed in the heart, and in experimental syphilis. In the days of exclusively mercurial treatment the drug was unjustly held responsible for some of the cases. The appearance of the arsphenamines in the therapeutic field with their higher hepatotoxic effect has, however, altered the etiologic background so far as drugs are concerned, as will appear in the discussion of the interpretation of jaundice in patients with syphilis. Many French authors, headed by Milian, believe that acute yellow atrophy in the patient with syphilis may be not so much the result of the primary or original infection, as of fulminating relapse, following inadequate treatment similar in its causal mechanism to the types of meningeal relapse which produce the familiar neurorecurrence. Of this Greenbaum has recently reported an excellent example, with unfortunately fatal outcome that might readily have been charged against arsphenamine had the drug been used.

The symptoms of syphilitic acute yellow trophy as described by Wile and Karshner, and confirmed in the patient Stokes has seen, are: insidious onset, with mild but steadily deepening

jaundice; malaise anorexia and vomiting, with or without fever may be an accompaniment. The patient complains of muscular aching and at times severe abdominal cramps. A toxic condition then supervenes, with emaciation and a typhoid state. Enlargement of the liver is noted at first, often an extreme degree for a short time, and, as the toxic symptoms increase, diminution in size is rapid. This shrinkage should be watched for from day to day by suitable marking. Ascites may appear early but usually develops as the liver shrinks. Hemorrhages from the bowel, hematemesis and purpura of the skin with petechial bleeding from the gums and buccal mucosa are not uncommon. As intoxication becomes more profound, psychosis with delirium, violent headache, and at times maniacal symptoms develop, or there is insomnia and depression. Apart from the deep jaundice the late symptoms suggest those of meningitis or uremia, with which latter condition those cases accompanied by severe nephritis are undoubtedly complicated. Wile notes the obstinacy of the constipation and the peculiarly offensive stool. Incontinence of urine and feces occurs just before death.

Laboratory aids to the diagnosis of acute yellow atrophy may be found in the presence of leucin and tyrosin crystals in the urine of most patients, although this finding is not invariable, and was absent in Stokes case. They may be extremely abundant and even cause precipitation. Tetrachlorphthalein tests of hepatic function show rapid decline, although this has no differential value since it occurs in all progressive changes. Bile from the duodenum may contain urobilin and urobilinogen in the hematogenous jaundice of the epidemic infectious type (p. 250). Urinary evidences of an accompanying nephrosis are not uncommon. A rising blood urea accompanies an unfavorably progressing case, possibly as result of the failure of the kidneys quite as much as of the liver

The treatment of early hepatitis is considered under the treatment of syphilis of the liver on page 872.

Subthreshold Hepatic Syphilis Recognized by Functional Tests.—It is of course extremely difficult to disentangle this question from the problem of injurious effects of arsenical medication on liver function. The literature as summarized by Elliott and Todd and concerned chiefly with the phenoltetrachlorphthalein and bromsulphonphthalein tests, has not revealed a particularly promising approach.

Friedenwald and Morgan found marked variations in the performance of known syphilitic livers. Brunsting pointed out that while single tests give untrustworthy results, repeated tests were more reliable. Ottenberg and Abramson had outright negatives in known syphilis of the liver. Irgang and Sala, using the icterus index and the van den Bergh test in 179 patients with active cutaneous syphilis, observed positive direct delayed reaction in 25 per cent and in 118 with secondary eruptions, positive reactions in 17 per cent. In 12 per cent of 134 cases with negative reactions t the outset, the van den Bergh test became positive during treatment but none developed clinical jaundice. Only 10 per cent of patients with positive tests at the outset, who received 4 to 8 doses of 0.9 Gm. neoarsphenamine, developed clinical jaundice. The majority returned t normal under treatment, indicating that a liver reacting to syphilis is not necessarily specially susceptible t an arsenical. They emphasize, however the necessity for prolonged observation and bismuth therapy of patients showing abnormal icterus indices and van den Bergh tests before treatment is begun. *Irgang (1937) again demonstrated the subthreshold therapeutic* shock and paradox demonstrable by functional test, to emphasize the necessity for caution and the use of bismuth in treatment. In reviewing hepatic complications in the pregnant syphilitic woman, he emphasized the importance of considering jaundice in pregnancy as due to the pregnancy and not to the syphilitic hepatic process. He believes that the pregnancy should be terminated.

There can be no question of the desirability of further development of this field with a view to detecting liver damage by syphilis in its earliest incipiency. A summary to facilitate the use of available functional tests is given in Figure 640

Hepatorecurrence.—The conception of relapse involving the liver as a more or less localized manifestation has been largely established by the energetic advocacy of Milian, who has insisted on the deleterious or activating effect of subtherapeutic dosage of the arsphenamines, and the danger of fal-

Fig. 640.

LIVER FUNCTION TESTS

(Modified from Steigmann, Popper and Meyer J.A.M.A., Vol. 12, pp. 279-285, 1943, with additions)

Test.	Normal reading.	Deviation.
1. Bilirubin in urine.	Negative.	Daily quantitative tests indicated in parenchymatous disease.
2. Urobilinogen in urine.	Trace.	
3. Van den Bergh reaction.	Negative.	
4. Icterus index.	4–6 units.	
5. Galactose tolerance test.	Over [illegible] Gm. in urine indicates decreased function.	Abnormal intestinal absorption modifies results.
6. Oral hippurate excretion test.	Equivalent of less than 3 Gm. of sodium benzoate in the urine indicates decreased function.	Intestinal absorption does not interfere. Liver damage roughly inversely proportional to hippuric acid excreted.
7. Blood proteins.	7 Gm./ml.	Decreased in some cases of chronic liver disease.
8. Albumin-globulin ratio.	2 : 1	Decreased in some cases of chronic liver disease.
9. Prothrombin response to vitamin K.	Normal prothrombin time 18–20 seconds (Quick).	In many cases of liver disease prothrombin level low and response to administration of vitamin K slow or incomplete.
10. Cephalin-cholesterol flocculation.	Normal standard.	Density of flocculation roughly proportional to liver damage.
11. Colloidal gold test.		
12. Takata-Ara test.		
13. Alkaline phosphatase test.	2.5–5 units.	Increase indicates roughly degree of biliary obstruction. Should be used in conjunction with cephalin-cholesterol flocculation test.
14. Azorubin-S test.	Dye appears in 30 minutes in duodenal drainage.	
15. Nonprotein nitrogen.	[illegible] mg %.	Rise indicates liver failure. May be due to associated renal damage.
16. Millon test.	Negative.	Tyrosine appears in urine in severe liver damage (acute yellow atrophy).
17. Cholesterol-cholesterol ester ratio.	2.	Abnormal 1 : 1 or less roughly proportional to liver damage.
18. Daily urinary output.		Diuresis indicates recovery.
19. Graham-Cole test.	Radiopaque concentration of dye in gallbladder.	
20. Bromsulphalein test.	Less than 5 mg. in serum after 30 minutes.	

Tests to Be Performed in Early Cirrhosis

1. Icterus index.
2. Urobilinogen in urine.
3. Bromsulphalein test.

Tests to Be Performed When Administering Hepatotoxic Drugs:

1. Icterus index.
2. Urobilinogen in urine.
3. Bromsulphalein test.
4. Cephalin-cholesterol flocculation test.
5. Hippuric acid excretion test.

Signs of Alarm (Liver Failure)

1. Rise of icterus index.
2. Millon test becomes positive.
3. Drop in prothrombin level, only partly relieved by administration of vitamin K.
4. Drop in cholesterol esters.
5. Rise in nonprotein nitrogen.

minating flare-up in patients who lapse after such treatment. While Milian's insistence on continued and larger dosage of the arsphenamines is not shared by other French observers such as Ravaut, Lortat-Jacob, Sézary and Simon, hepatorecurrence as a clinical conception akin to neurorecurrence for example is established. The essence of a hepatorecurrence is its onset, some weeks or even months after the suspension of a short, small-dosage course of an arsenical, unsupported usually by heavy metal. That such an outcome can explain some of the acute yellow atrophies previously ascribed to delayed arsphenamine poisoning is suggested by Greenbaum's typical case. The difficulty of differentiating the two may be inferred from one of Irgang and Sala's cases in which the circumstances might suggest a hepatorecurrence, but partial, though not complete recovery took place under sodium thiosulphate.

The "Latent" Liver.—Latent livers and spleens are asymptomatic, and are either overlooked in physical examination or discounted as of no significance (Fig. 667). It seems possible that, as with the spleen in early syphilis, they may even disappear without attracting anyone's attention. In the series of 419 patients (Fig. 642) of 40 patients who had enlarged livers 33 had positive blood Wassermann reactions. Of the 20 patients with both hepatic and splenic enlargement, 17 had positive blood Wassermann reactions. It is justifiable to suggest, therefore, that a serologic test is a necessary part of the medical examination of all patients who have palpable livers or spleens. The wider use of this hepatosplenic guidepost and suspicion arouser, as is apparent from *many cases studied, would lead to the recognition of* an appreciable amount of syphilis during latency rather than following the appearance of symptoms due to irreparable damage.

We have found Middleton's maneuver a valuable aid in detecting hepatic enlargement in patients in whom it might easily and in fact was previously overlooked. This consists in having the patient lie on the flexed right forearm, thus elevating the thoracic spine and anterior rib margin and thrusting the liver forward, emphasizing the edge and bringing it away from the ribs. The same maneuver assists in palpating the enlarged spleen (left forearm) but is less effective. Moore (1943) discounts the conception of latent or asymptomatic hepatic syphilis on the ground of autopsy rarity of syphilitic liver disease. Hepatic enlargement alone we agree cannot be accepted as diagnostic of syphilitic hepatitis in a benign or subthreshold stage without supportive clinical and laboratory evidence. Autopsy findings years after a benign process, however, do not necessarily establish or exclude mild types of involvement many years before. The life history of certain of our syphilitic patients observed for twenty years since the onset of their infection (see Fig. 641), clearly indicates that the early warning of an ultimate hepatic cirrhosis was given by the ups and downs of hepatic enlargement otherwise completely asymptomatic in the early years of the disease, coincident at times with the appearance and disappearance of positive serologic tests on the blood.

Late Diffuse and Localized Gummatous Hepatitis.—Slow chronic inflammatory and degenerative changes and fibrosis or cirrhosis of the liver are to be expected among the clinical manifestations of syphilis, both inherited and acquired. Localized gummas vary in size from multitudes of pinhead-sized lesions to large single gummas with extensive necrosis and secondary change. Both types of lesions may develop simultaneously, the clinical behavior of the case varying with the proportion that interstitial fibrosis bears to localized gumma formation at a given moment. Part of the clinical picture in any given case will depend on the location of cirrhotic and gummatous lesions with respect to important structures within and without the hepatic and biliary systems. A large gumma projecting into the portal fissure may produce ascites by pressure on the portal vein; thousands of miliary gummas, a *diffuse inter-*

Fig. 641

"LATENT LIVER" DEVELOPMENT OF HEPATIC CIRRHOSIS IN SYPHILIS

Date		Liver enlarged	Spleen enlarged	Serology	Remarks
[illegible]	June				Primary lesion and secondaries.
[illegible]	October				Recurrence.
[illegible]		–	–	+	
[illegible]	May			Neg.	
[illegible]	January			Neg.	
[illegible]	March	+++	–	+++	No other signs hepatic disease.
[illegible]	March (late)	++	–	++	Drinking heavily
[illegible]	December	+	–	+	Provocative positive.
[illegible]	February	–	–	–	Treated 606-Bi.
[illegible]	June			–	Treated 606-Bi.
[illegible]	October	+	–	–	Treated 606-Bi.
[illegible]	June	–	–	–	
[illegible]	October	–	–	–	Intensive treatment.
[illegible]	June	–	–	–	Intensive treatment.
[illegible]	December	–	–	–	Moderate drinking.
[illegible]	February	–	–	–	
[illegible]	December	±	–	–	
[illegible]	January	–	–	+++	CSF neg.
[illegible]	March			–	After 18 Bi-sal.
[illegible]	October			–	
[illegible]	January			+++	Re- or superinfection.
[illegible]	January	++	–	+++	Darkfield positive penile lesion.
[illegible]	February			+++	
[illegible]	March				Posterior coronary thrombosis.
[illegible]	April			+++	Soluble Bi.
[illegible]	October			+++	Intermittent treatment abroad.
[illegible]	April	++	++	+++	Stopped alcohol, diet.
1941	September	+	+	+++	Bismuth, iodide.
[illegible]	June			–	Continued Bi.
[illegible]	October	±	±	–	Continued Bi.
[illegible]	May	±	±	+	
[illegible]	June			–	Rest period.

An eighteen-year relapsing and progressive history of syphilis: serologic relapses associated with [illegible] recurring hepatic enlargement; (b) re- or superinfection; (c) coronary thrombosis. Repeated response of hepatic enlargement [illegible] treatment (therapeutic test). Final appearance of splenomegaly (1941). Therapeutic response of both liver and spleen to syphilotherapy (serologic response simultaneously) plus diet and stopping of alcohol. Alcohol probable factor throughout. Clinical picture that of Laennec' cirrhosis. At no time has the patient been jaundiced there has been no recognizable ascites, and his icterus index and functional tests are recently (1941–1943) normal.

stitial fibrosis, or the contraction of a gummatous scar may be equally effective in blocking the portal circulation within the liver and bringing about ascites. Jaundice may arise from diffuse interstitial hepatitis with blocking of the finer bile ducts. It may likewise arise from the pull of a band of fibrous tissue, the distortion of a scar or the pressure of a fresh gumma which kinks or blocks the hepatic duct.

Portal cirrhosis (Laennec) nodular cirrhosis and atrophic cirrhosis of the liver include in varying degrees and in varying proportions of cases, the diffuse gummatous and gummato-fibrotic syphilitic process in the liver The studies by Schumacher (1937) of Laennec's cirrhosis, including one case of smooth hypertrophic cirrhosis of the Hanot type, well illustrate the interplay of influences involved in this group of hepatic cirrhoses. Of 45 cases of acute cirrhosis, including 44 of nodular or Laennec cirrhosis and one of Hanot cirrhosis, 28.8 per cent had presumptive evidence of syphilis, approximately one-third were known to have used alcohol in excess, or approximately one-half if those cases were excluded whose alcohol habits were unknown; and 11.1 per cent were both syphilitic and alcoholic (15 1 per cent when unknowns were excluded) Approximately three-quarters of the cases of acute cirrhosis and all of those with acute cirrhosis and syphilis were in men. Among the cases in which the duration of infection was known—that is, in less than half of them—there was no instance in which syphilis had been present for less than ten years. A control group of 45 autopsies with no cirrhosis in persons of the same age and sex as those with acute cirrhosis showed that two (4.4 per cent) had had syphilis; and two had used alcohol in excess. The two factors were combined in no instance. In a group of 21 autopsies

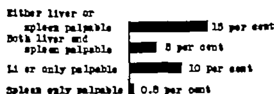


FIG. 642.—THE "LATENT" OR PALPABLE LIVER AND SPLEEN AS A GENERAL DIAGNOSTIC AID IN LATE SYPHILIS (419 CASES, RECOGNIZED SYPHILITIC HEPATITIS EXCLUDED).

of persons with syphilis, diffuse cirrhosis of the liver was found in three cases (14.3 per cent). Syphilis, therefore, long continued in association with alcoholism, and perhaps alone, may cause diffuse cirrhoses of the liver

Imitative Possibilities of Late Hepatic Syphilis.—The combination of a generalized lesion such as syphilitic interstitial hepatitis, and a localized lesion such as gumma, with inflammatory extensions (perihepatitis) to surrounding structures, can produce syphilitic imitations of every imaginable clinical entity medical and surgical in which the liver may be involved. From the standpoint of clinical pathology there may be, during the period of active infiltration, a large firm liver heavier than normal smooth, and glistening. Since the process is rarely without certain spots of localization, a few small gummas may be recognized, or there may be patches or masses of heavier unencapsulated or uncircumscribed infiltration. As time elapses, such a liver depending somewhat on the interrelation between extension and healing, as in all syphilitic lesions, may shrink and become hard and atrophic it may shrink slightly but increase in firmness or it may shrink most in those parts in which infiltration with gummatous tissue was most pronounced thus giving rise to *ridges, depressions, and irregularities not amounting to* actual lobulation, in a liver larger than normal, but not as large as in the first months or years of the involvement. Interference with the circulation may vary widely with these various changes, and a small liver does not necessarily mean an obstructed circulation, nor a large one a free portal return. If large local gum-

mas predominate over diffuse infiltration or if they are, as occasionally the only manifestations, the mass becomes the conspicuous clinical symptom. The dragging of a small lobe into the field usually occupied by another structure, the granulomatous left lobe for example, suggests to the clinician a spleen, a kidney the head of the pancreas, and so forth (Fig. 669) As gummas involute, deep clefts from scarring contracture take their places, producing two or more lobes where one was before, the so-called *hepar lobatum*. A diagnosis of *hepar lobatum* can never be regarded as excluding a collateral diagnosis of varying degrees of interstitial fibrosis or cirrhosis.

Perihepatitis.—Extensions of localized inflammatory processes from the parenchyma of the liver to the peritoneum over its surface are common in cases of syphilitic gumma. The immediate result, as in syphilis of other peritoneum-covered viscera, is adhesions to surrounding structures with varying degrees of distortion as the adhesions toughen and the original inflammatory process subsides with shrinkage. In this manner the portal fissure may be almost obliterated and the gallbladder lost in a mass of inflammatory tissue whose constricting effect and secondary inflammatory involvements become apparent in symptoms of biliary tract obstruction and cholecystitis (Figs. 661 673)

Diffuse perihepatitis may involve the entire liver with thickening of the capsule and extension to the parietal peritoneum. With these exacerbations of peritonitis, no less than with the softening of larger gummas and the waves of exacerbation in the gummatous infiltrative process, attacks of fever and pain occur which are highly deceptive to the clinician because associated in his mind only with nonsyphilitic infectious processes. Such attacks were an important feature of the symptoms in a number of our cases.

Involvement of Gallbladder and Ducts.—Involvement of the wall of the gallbladder and the ducts by an actual late syphilitic process, a gummatous cholecystitis, appears unknown. The clinical pathology in some of the cases in which operation is performed and the portal fissure is found blocked by adhesions, and the gallbladder buried, suggests the possibility that the wall of the gallbladder may have been secondarily involved in a gummatous infiltrative process beginning elsewhere, but there is as yet no support, pathologically for such a view

Involvement of the Lymphatic System.—Involvement of the lymphatic system must be borne in mind in connection with the clinical pathology of late syphilitic hepatitis. Satellite groups of inflammatory lymph nodes are often seen in the vicinity of the areas of gummatous activity in the neighborhood of the portal fissure, and may promote obstruction or suggest malignant change.

Predisposing Factors in Hepatic Syphilis.—Rolleston observed the prejudicial effect of alcohol, malaria, and previous jaundice (presumably infectious) in favoring late syphilis of the liver Warthin has emphasized the low-grade hepatitis which he observed in a large proportion of patients with syphilis to whom arsenical treatment had been administered. O'Leary has pointed out the increased likelihood of hepatic complications in the course of infections in which a jaundice has occurred whether precipitated by treatment or intercurrent. Of this we have seen what we thought were fair examples. In view however of the complexity of the factors involved, and of the fact that there does not at the moment appear to be a wholesale increase in clinical late hepatic syphilis corresponding to the second decade of the arsphenamine era,

we are inclined to doubt the great importance of the drug as predisposing to hepatic syphilis. Rather it seems to us we are dealing with syphilitic hepatic involvement dating in most cases from the early months of the disease than syphilitic hepatic involvement created out of a clear sky by the influence of a drug We have gathered from repeated examinations of patients, the impression that syphilis of the liver itself runs this lifelong course now above now below the symptomatic threshold and that only patients with an initial hepatic localization appear to make the unfortunate responses to other agents. In other words, the arsenical is not creating new hepatic syphilis it is perhaps, though not probably bringing occasional cases to the surface of clinical recognition.

The Instrumentality of Syphilis in the Production of the Banti Syndrome of Hepatic Cirrhosis with Splenomegaly and Anemia.—This subject has been critically examined by Korns. From his thoroughgoing review Korns reaches the conclusion that the Banti syndrome may be but is not necessarily always caused by syphilis. In fact, he contests outright the views, such as those of Norris, Symmers, and Shapiro to the effect that the disease is invariably syphilitic.

From 170 cases, many of them frequently cited in the literature, Korns was able to select only 36 in which the authenticity of the syphilis and the Banti syndrome was incontestable, and 30 in which it was questionable, thus discarding 104 cases in which no relationship was satisfactorily established. I the syphilitic cases the sclerogummatous form occurs most frequently The liver is reduced in size (weights as low as 700 Gm. have been recorded) and is so widely fissured and lobulated by linear and stellate cicatrices, the residua of healed gummata, that the shape of the liver may be altered out of all recognition. Rolleston ttributes the splenomegaly to amyloidosis or gummatous infiltration, but Korns believes from study of autopsy protocols that simple interstitial fibrosis is the usual picture. Cheadle statement that syphilis is the most important cause of perihepatitis is accepted by Korns as applicable to the thickening of Glisson capsule and the dense and extensive synechias to the diaphragm and adjacent viscera which are of almost universal occurrence in syphilitic Banti's syndrome. The blood picture of secondary anemia, leukopenia and relative lymphocytosis characteristic of Banti' syndrome is found in tertiary hepatic syphilis terminating in the Banti syndrome. Intermittent jaundice, usually mild, and generally obstructive in type; recurrent ascites, hemorrhage, either from the nose or stomach and pain in the upper quarters of the abdomen, are of frequent occurrence The pain is regarded as particularly important as symptom of syphilitic hepatitis.

Korns emphasizes the fact not only that all patients with Banti's syndrome in whom the presence of syphilis can be established should be treated for the disease but that all cases of Banti s syndrome without exception should be subjected to therapeutic test, prolonged and vigorous, before syphilis is finally excluded. Time and again, as he says, in the literature this consideration has been overlooked because of the absence of unequivocal physical signs or confirmatory serological tests. He emphasizes, as will be noted again later the large proportion of these cases that have done well under arsphenamine therapy

THE CLINICAL DESCRIPTION OF LATE HEPATOSPLENIC SYPHILIS AS ILLUSTRATED BY A STUDY OF 73 CASES

In order to secure a fresh impression of the problem which syphilis of the liver presents to the general diagnostician a review of 73 cases in the files of the Mayo Clinic diagnosed as syphilitic hepatitis was undertaken. The material proved to be rich in surprises, and a large proportion of the cases had taken falls out of one or another diagnostician including the syphilologist. Three

were cancers, and 2 were cirrhoses, apparently nonsyphilitic in type,* although associated in one of the cases with a positive blood Wassermann reaction and in the other with a history of syphilis and much treatment.

In accordance with the usual recorded experience in hepatic syphilis, the proportion of women affected, considering the incidence of the disease, was higher than men; 31 women to 30 men, although with the usual incidence ratio, the men should have been much more numerous. McCrae for example found 66 men to 34 women. More than half were in the fifteen-year period of middle life, thirty-five to forty-nine years. In 37 or about half the cases, the duration of the infection was known, and 75 per cent of the patients were in the first and second decades, 35 per cent in the former and 40 per cent in the latter. This makes syphilitic hepatitis one of the earlier of the late complications of syphilis. Three cases ranged in duration from two to four years, representing probably chronic extensions of mild early hepatitis, that did not come under observation.

Distinct mass felt	53 per cent
Liver enlarged much	47 per cent
Tender on pressure	32 per cent
Right-sided enlargement	18 per cent
Mesial enlargement	17 per cent
Left-sided enlargement	13 per cent
Nodular	18 per cent
Mass called right kidney	7 per cent
Mass called gall bladder	6 per cent
Mass called tumor of splenic flexure	1 per cent
Distinctly hard	25 per cent
Distinctly soft	3 per cent
Fixed	3 per cent

FIG. 643.—PHYSICAL CHARACTERISTICS OF THE SYPHILITIC LIVER.

Cachexia and Jaundice.—The appearance of the patient with a syphilitic hepatitis may vary from the most robust good health to a cachexia suggesting a malignant cause. Persistent jaundice is less suggestive of syphilis than of malignant or obstructive conditions.

Sixteen per cent of our patients were jaundiced on first sight—a small proportion. Attacks of jaundice of varying length occurred in an additional 20 per cent (total) and a few had been continuously jaundiced since onset (11 per cent). More than a third of the patients were described as undernourished or emaciated (37 per cent) and weight losses from 2 to 50 pounds were recorded. Gain in weight, stationary weight, or slight loss were frequently observed in very sick patients with marked emaciation, due to the accumulation of fluid in the abdomen and the enormous mass of the liver or spleen. Half of the weight losses ranged between 10 and 25 pounds, so that the constitutional disturbance capable of being produced by this form of syphilis can be rated as considerable.

Physical Characteristics of the Liver (Fig. 643).—The right lobe is the seat of tumefaction in about 18 per cent, and a surprising proportion of the

* J. E. Moore states (personal communication) that he has examined two patients one with syphilitic Banti syndrome and the other with acute hepatitis, jaundice, palpable liver, and fever in both of whom a loud systolic thrill and bruit could be heard over the liver. In both cases aneurysm of the hepatic artery was suspected, but the sign disappeared immediately upon the institution of treatment.

palpable change when localized occurred in the epigastrium and to the left (28 per cent) McCrae has emphasized the importance of left lobe enlargement in diagnosis (49 of 89 cases) and Friedenwald and Morrison found that gumma most often presents at the epigastrium. The fixation of the liver by perihepatitis is a point always to be borne in mind, because it deprives the clinician of the important aid of association of the tumor with respiratory excursion, and hence with liver or diaphragm.

Enlargement of the spleen will be seen to have occurred in 46 per cent of the cases McCrae found it in 50 per cent of his patients.

The nodular liver has not been conspicuous in our experience, although a distinct mass was common finding, producing irregularities in outline. Some of the minor items are of interest as indicating the sources of error the examiner apparently not seriously considering the possibility of a general involvement of the liver in certain cases, so definite was the tumor and so deceptive its characteristics. Fixation of the mass by perihepatitis was the probable cause of error in Fig 608 in which diagnosis of retroperitoneal sarcoma was made

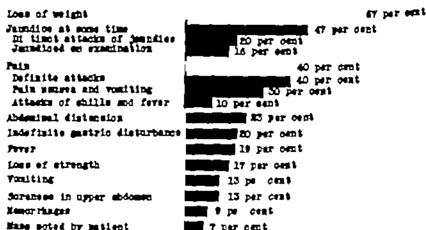


FIG. 644 —THE SYMPTOMS OF HEP TIC SYPHILIS.

Loss of weight and jaundice in 60 per cent of cases in which there is definite history of attacks, pain, nausea, vomiting, chills, and fever are more prominent than distention (field), stomach trouble, and hemorrhages, which are the earmarks of cirrhosis.

Syphilis of the liver can exist without palpable enlargement and with favorable response to treatment. The proportion of cases in which the spleen is not palpable ranges with fair impartiality through all grades of involvement of the liver from normal size to a free border at the iliac crest.

The uniformity of distribution of the splenic enlargement, so generally regarded as an accompaniment of syphilitic cirrhosis rather than of gummatous hepatitis, confirms the impression that the size of the liver of a patient with syphilis is not measure of the degree of cirrhosis which exists, and furthermore that some degree of cirrhosis is common accompaniment of cases in which gummatous masses are the chief presenting sign. The attempt to base clinical diagnosis of the type of syphilitic involvement on physical signs has a liberal margin of error owing to mixed types, although, in general, masses and lobulation are, of course more suggestive of preponderantly gummatous change.

Symptoms and Diagnosis.—Taken in the aggregate without a hypothetic distinction between cirrhosis and gumma, the symptoms of syphilis of the liver (Fig 644) bear a striking resemblance to those of infectious and malig-

nant processes, cholecystitis, cholelithiasis, and perihepatitis. On a symptomatic basis, as well as on signs, gumma is the more conspicuous type of syphilis of the liver although observers such as McCrae and Wile emphasize cirrhosis.

Unquestionably the performance of a routine blood serologic test and the taking of a careful history on all abdominal complexes will increase the apparent incidence of gumma, which has been cloaked under the symptomatic picture of acute hepatic and biliary infections, and may lead to a reduction in the relative clinical prominence of cirrhosis.

Loss of Weight.—Weight loss by untreated patients cannot be taken as having much influence in swinging the diagnosis from syphilis toward malignancy While in general the patient with a mass of syphilitic origin is likely to be in good condition, severe cachexias, with rapid improvement, are not uncommon with hepatic syphilis.

Jaundice.—A persistent, slowly deepening jaundice is suggestive of malignancy The jaundice of syphilitic hepatitis is usually mild and periodic in character It may be produced by exacerbations of hepatitis, and be nonobstructive or it may be typically obstructive with acholic stools, and be due to pressure of lymph nodes or gummas, torsion or constriction from adhesions along the course of the ducts. A persistent slight jaundice may result from interference with the patency of a large bile duct in the liver itself

Pain.—The pain of syphilitic hepatitis is often spoken of as "typical liver pain" in the right hypochondrium but the term is unsatisfactory since radiation to the shoulder seems usually to suggest disease of the gallbladder Prominence of high backache suggested duodenal ulcer twice, and low backache suggested renal colic once, in this series. Definite substernal pain with left-shoulder radiation suggested angina pectoris in a physician who had no cardiovascular lesion and who recovered immediately when his "gallbladder" was treated for syphilis. While the steady pain may be gnawing and described as gastric distress, or a sense of heaviness and weight, the possibility of occurrence of definite attacks in late hepatic syphilis should be borne home vigorously to all who have occasion to make diagnoses of upper abdominal lesions. An attack of syphilitic hepatic or perihepatic pain may be indistinguishable from that of cholecystitis or cholelithiasis. It may come on abruptly be brought on by exertion, be somewhat relieved by pressure last for hours or days, disappear abruptly and leave a tender or sore spot for hours or days. When with this typical gallbladder pain there is associated vomiting, chills, and fever it is small wonder that cholecystitis is the usual first thought, and that a mass in the right subcostal region is interpreted as a distended gallbladder and opened to the chagrin of the surgeon. It was with good reason that Rolleston made it a dictum that every patient with well-marked signs of tertiary syphilis and probable cholelithiasis should have mercury and iodides before operation. In present-day practice the well-marked signs of tertiary syphilis should include blood serological tests in all cases of upper abdominal complaints before operation, as the least measure of precaution against error

Fever —Fever occurred in only 18 per cent of the patients in the series, although it is spoken of as common. It is a probable associate of the softening of gummas, and of perihepatitis and local peritonitis. While resemblances to tuberculosis, typhoid and malaria are noted, in half of the cases there were definite attacks preceded by chills. The rise may be small and of short duration, and almost instant response follows the first administration of arsphenamine.

In one case of longstanding syphilis of the liver a striking febrile Herxheimer reaction was noted In febrile cases with an underlying breakdown of gumma, pointing of the lesion with drainage into the pleural cavity and empyema, has been observed (Rolleston)

Ascites.—Patients who accumulate fluid form a more or less distinct group symptomatically (Fig. 645) which confirms the impression that their condition is a reflection of the special pathology of syphilitic cirrhosis Ascites, especially if transient, may however be the result of perihepatitis and peritonitis, beginning at the site of a gumma, or of obstruction of the portal vein in the portal fissure by pressure. Transient obstruction of the portal circulation by an acute diffuse exacerbation of chronic interstitial hepatitis with accompanying tran-

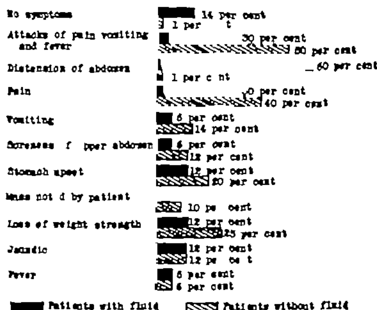


FIG. 645 —COMPARISON OF SUBJECTIVE COMPLAINTS IN P TIENTS WITH HEP TIC SYPHILIS Patients who accumulate fluid have fewer conspicuous complaints and more insidious course than those who d not.

ment jaundice may lead to the intermittent ascites, which McCrae regarded as distinctive of syphilis of the liver Comparatively small livers are commoner in the absence of ascites than with it, so that the clue to the cause is to be found not so much in the mere size of the liver as an index of cirrhosis as in the intimate pathologic condition which it is seldom possible to analyze clinically The large liver may be the seat of a diffuse obstructive process which blocks the portal return, or of an inflammatory process which sets up peritonitis or local obstruction, even more frequently than the supposedly contracted small liver

In Stokes study of ascites in the present group of cases, the observations, summarized in Figs. 645 and 646 were made. Ascites is not common complaint of syphilitic hepatic disease in the aggregate, being present in only about one third of an verage series such as ours. Normal or only slightly enlarged livers occurred in 36 per cent of cases of ascites, and large livers in 51 per cent; in the remainder the liver was medium sized (6 cm. below the costal margin). On the other hand, normal or only slightly enlarged livers occurred in 50 per cent of cases in which there was no ascites, and very large livers in only 14 per cent.

Symptomatically the patient who develops ascites is a less clamorous claimant for medical attention than is the one who does not accumulate fluid The onset is likely to be *insidious, and the first warning simply* a distention of the abdomen (Fig. 645) Attacks of various types, pain, loss of weight and strength, and gastric upsets, all seem to be more conspicuous when patients remain free from fluid. This again points to the cirrhosis as the most common cause of ascites. Localized gumma produces the more stormy symptoms, al though again the size of the liver need not be an index of the degree of cirrhosis, or at least of portal obstruction. Jaundice and ascites showed no constant relation that was detectable in this series of cases, the former occurring as often with the latter as without.

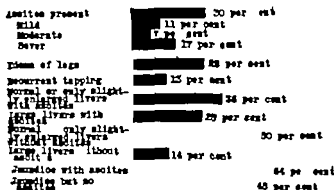


FIG. 646.—FINDINGS ASSOCIATED WITH ASCITES.

Evidently it is not the small liver that produces ascites. The proportion of large livers is higher in ascites and lower in its absence. Jaundice and ascites show no interrelation.

It has been suggested that fluid is the result of longer duration of the syphilitic involvement, with corresponding tendency to cirrhotic contracture. In the aggregate we could not find any significant difference in the duration of either infection or symptoms in the cases in which there was no fluid. The complexity of the factors involved evidently defeats generalization of this sort.

The Alcohol Factor —Chronic alcoholism long regarded as the cause of a special type of cirrhosis, and as contributory to the cirrhotic manifestations of hepatic syphilis, has lately been refused recognition by Wile and experimental reproduction of an alcoholic cirrhosis seems to have been impossible *in animals (Robertson) It is our clinical impression* however supported by cases such as Figure 641 and Schumacher's observations, that alcohol is definitely influential as a facilitator in the production of hepatic cirrhosis in syphilis. McCrae found that 62 of 70 patients used it freely but this does not, of course prove a causal relationship The examination of this point in the Mayo Clinic series, while inconclusive because of the small number of patients who used alcohol (22 of 70) suggests that while alcoholics show no distinctive effects of the drug in the size of their livers, and alcohol is not necessary to the production of a full-fledged syphilitic hepatitis, the regular and heavy drinkers are none the less definitely more often the victims of ascites (Fig. 647) and have a correspondingly worse prognosis than nonalcoholics (Fig 658) The mechanism of such an action, if it exists, is too complex for definition in a clinical study

Hemorrhage.—Hemorrhage is generally accepted as more common in cirrhotic contracted livers as the product of the rupture of the varices developing with vascular obstruction

Seven of this series of patients (10 per cent) had hemorrhages as definite feature of their course. Six vomited blood, and two passed blood by stool in recognizable amounts. The livers of all the patients were not enlarged, or only slightly enlarged, suggesting the cirrhotic factor. The spleens were variable, from normal to greatly enlarged (Banti syndrome) Three of the 7 patients had had marked ascites. The possibilities of diagnostic confusion which center around this symptom are interestingly pictured by Fig 678. A second case in which duodenal ulcer

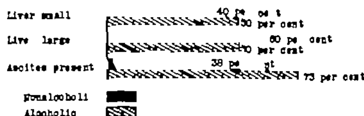


Fig. 647.—Size of Liver and Presence of Ascites in Alcoholics and Nonalcoholics

Although alcoholism does not seem to influence the size of the syphilitic liver markedly ascites is definitely more marked in alcoholics with syphilitic hepatitis.

had been diagnosed by roentgen ray was found. Dietary measures failed to give relief, and the patient died later of repeated hemorrhages following treatment for syphilis, in which it is possible that rapid shrinkage of the liver and portal obstruction combined to produce the hemorrhages without the presence of duodenal ulcer Such possibility of error in diagnosis deserves further study

The Blood Picture.—The blood picture (Figs. 648, 678) associated with the hepatosplenic complexes revealed the widest range of variation and the most interesting possibilities from the standpoint of diagnosis, but showed no

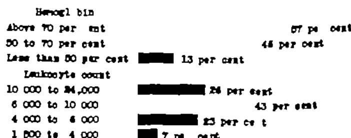


Fig. 648.—Blood Picture in Cases of Syphilitic Hepatitis.

There is no constant relation between size of liver and spleen and blood picture. There is no constant relation between leukocytosis and fever

constant relation between the blood findings and the physical findings. The simulation of Banti's cirrhosis with splenomegaly and of splenic anemia with anemia, leukopenia, and splenomegaly was illustrated by 2 cases.

In the first case a man with a hemoglobin of 36 per cent, erythrocytes 2,670,000, and leukocytes 6700, had a greatly enlarged spleen and slightly enlarged cirrhotic liver The patient had had hemorrhages. There was marked ascites, coming on two years after intensive arsphenamine treatment. The blood Wassermann reaction was positive, and the history of syphilis quite definite. No further treatment was undertaken and the patient subsequently died, without necropsy Clinically at least, he had typical Banti's disease associated with syphilis. As Rolleston remarks,

the fact that a patient in the hepatic cirrhosis group does not respond to treatment for syphilis does not disprove the ultimate syphilitic etiology since the damage to metabolism and the introduction of incidental or secondary factors due to lowered resistance may be enough in itself to tip the scale toward a bad result.

The second case, man with hemoglobin of 83 per cent, a red blood count of 3,080,000, and white cell count of 1800, had greatly enlarged spleen, but the liver was not palpable. There was no ascites and there had been no hemorrhages. Although the blood Wassermann reaction was repeatedly positive, there was no history of syphilis. Treatment was refused, and none had been given previously The patient died elsewhere, without necropsy Clinically the condition belongs rather with the splenic than with the hepatic group, and must be regarded as not proved so far as syphilitic etiology is concerned.

The possibility of deception afforded by nephritis or other extrinsic cause for anemia in a patient with syphilis and hepatitis is illustrated by woman with hemoglobin of 30 per cent, a red blood count of 3,000,000, and white blood count of 10,400, who had greatly enlarged cirrhotic liver large amount of fluid, compensated aortic lesion, and marked nephritis. A most favorable temporary response followed mixed treatment for syphilis by mouth.

Pseudopernicious anemia symptomatically at least, associated with hepatitis and splenitis, is illustrated by the case of woman with hemoglobin of 80 per cent, sore mouth, diarrhea, and achlorhydria. The liver was greatly enlarged, the spleen only palpable. The red blood cell count, however established the secondary character of the anemia (3,850,000, with a color index of 0.4) The white blood count was 6500, the blood Wassermann reaction was weakly positive in the first test and strongly positive thereafter The response to treatment was very gratifying, although, as is often the case the persistence of slightly subnormal hemoglobin and red cell count for several years was observed.

The Kidney —An early impression to the effect that the kidneys of patients with severely involved livers were unusually sensitive to treatment irritation was not borne out by this survey In fact, the normality of the renal mechanism was remarkable in a group in which, with extensive damage to the liver one should expect a high incidence of amyloid degeneration.

In only 1 case did the persistent presence of large amount of albumin with comparatively normal renal function suggest the existence of an amyloid degeneration, and this patient recovered completely with three years of treatment. The liver was greatly enlarged, but the spleen was not palpable. That the nephrosis was not entirely due to amyloid, but more probably to the effect of chronic focal infection, was suggested by the improvement which followed the extraction of number of apically infected teeth. A second patient had chronic cardiorenal complex. Only 2 other patients, besides those mentioned, disclosed definite evidence of renal irritation during treatment, an unusual showing even for young and robust persons, and not t all suggestive of marked damage to the kidney by changes associated with syphilitic hepatitis and splenitis.

SYPHILOLOGICAL FINDINGS IN SYPHILITIC HEPATITIS

The prop of clinical diagnosis in hepatic disease, so far as syphilis is concerned (Fig. 649) is the blood serologic reaction, which has reduced greatly the time requirements and exactions of the former diagnosis by therapeutic test. It has, at the same time extended equally our comprehension of the deceptive possibilities of clinical syndromes. The frequency with which in this series at least, the blood serologic reaction, routinely applied to all patients with complaints referable to the upper abdomen, would have prevented a diagnostic misinterpretation or a disappointing surgical intervention, was instructive. Nothing less than the application of the blood serologic tests before operation to every patient with a surgical lesion of the abdomen would protect the patient from error in diagnosis of syphilitic liver and biliary tract disease That the therapeutic test must follow the finding of the positive serologic reaction in certain cases in order to eliminate the possibility of mere coincidence is as true now as in the day of Rolleston s dictum. Every patient who has

repeated strong positive blood serologic reactions with a hepatosplenic syndrome or a gallbladder syndrome is entitled to a therapeutic test before operation unless he is a critical surgical emergency From the case records it will be apparent that this dictum should be extended to include patients with symptoms of pancreatitis and pancreatic tumor mesenteric tumor and so forth. The service of the blood serologic reactions in these cases is to release us from the uncertainties of palpatory diagnosis, so far as syphilis is concerned, or at least to bring syphilis constantly into the field of suspicion. As such it should be fully utilized. The reduction in incidence of diagnostic error in this group of syphilitic patients in the Mayo Clinic after the adoption of the routine blood serologic test on all surgical patients was very marked

False Negative Serologic Reactions in Syphilitic Hepatitis.—Figure 649 presents the relative importance of the various items which constitute an examination for syphilis in the hepatosplenic group of cases.

False negative serologic reactions and fluctuating returns must be expected at times, whether of intrinsic or technical origin, in syphilis of the liver

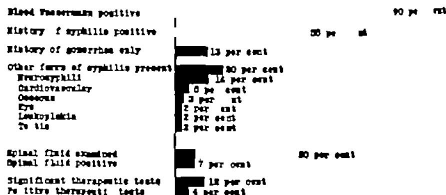


Fig. 649 —Syphilological Findings in Syphilitic Hepatitis.

McCrae found 8 negative cases in 41 of hepatic syphilis and 2 in 73 late cases appeared in this series.

The high incidence of positive blood serologic reactions is not, merely the result of serologic diagnosis, but of genuine trend to uniform positiveness with reasonably sensitive technic in a very large proportion of cases of hepatic syphilis. For some years, in watching the run of such cases through the Mayo Clinic, Stokes was almost convinced that a negative blood Wassermann reaction, repeatedly obtained, excluded syphilis of the liver outright. In studying this series of cases, however two examples of persistent Wassermann negativity one confirmed by operation as syphilitic hepatitis, the other by completely successful therapeutic test, were found. A third case that of physician who proved by therapeutic test to have syphilitic gallbladder syndrome, had negative blood Wassermann reaction repeatedly before coming to the clinic, and had received diagnoses of angina pectoris, and gallstone colic, accordingly His test was repeatedly positive with the Kolmer technic, and he had definite history of digital extragenital infection with scar The response t treatment as immediate, operation being rendered unnecessary

False Positive Serologic Reactions in Carcinoma of the Liver—The question of a false positive tendency in the blood serologic test in carcinoma of the liver is important and, so far as our experience goes, can be answered in the negative. It is, however almost impossible to prove the absence of syphilis clinically in a patient with repeatedly positive blood serologic reactions and cancer of the liver short of necropsy and, even then, because of the fact that

syphilis of the liver occupies the early middle period of the average lifetime of a patient with syphilis there may be little to clinch the diagnosis in the general pathologic findings.

In investigating the possibility of obtaining false positive blood serologic reactions in carcinomatous involvement of the liver the records of 168 patients who had come to autopsy at the Mayo Clinic with carcinomatous livers were examined. In this group 2 had strong positive blood serologic reactions, an incidence of 1 8 per cent and one a weak positive. One of the 3 patients had an incontestable syphilis of the nervous system with positive spinal fluid in addition to the positive blood (Fig 671) and the postmortem findings of the second strong positive case were incomplete. The weak positive was unsupported. In any case the incidence of definite false positives scarcely exceeds the margin of error which may ordinarily be expected of the average serologic test.

Nonspecific Effect in Nonsyphilitic Hepatitis.—We have seen nothing to lead us to suspect a nonspecific effect on hepatitis of nonsyphilitic origin from arsphenamine other than the apparent shock in Fig 671 In fact, the nonsyphilitic liver as in cases of cancer or in what appears to be a nonsyphilitic cirrhosis, responds unfavorably or the process advances at the usual rate without response.

Collateral Evidence in Diagnosis.—The examiner cannot hope to secure assistance from collateral clinical findings, excluding the blood Wassermann test, in more than 20 to 25 per cent of his cases. The conspicuous exemption of the nervous system has been a matter of comment among observers in pre-Wassermann days, and the cardiovascular system seems likewise to be protected to no small degree. The other protective" groups of structures, such as the bones and the skin are also remarkably free from involvement and may be imagined as not having been drawn on for physiologic defence because of the efficiency of the liver and spleen in supplying a protective mechanism. Because of the probable high incidence of Wassermann positiveness in cases of syphilis of the liver the relative value of the history of syphilis can be fairly judged, and does not greatly exceed 50 per cent, as compared with 90 per cent for the blood test. The interpretation of and methods for applying the therapeutic test in suspected cases of syphilis of the liver will be discussed under the head of treatment.

The Differential Diagnosis and Sources of Diagnostic Error in Late Syphilis of the Liver—Rolleston's monograph described seven common sources of diagnostic error in connection with late syphilis of the liver applicable to the diagnostic problems of pre-Wassermann days. These included (1) symptoms of syphilis of the liver suggestive of portal cirrhosis, or simple chronic peritonitis and perihepatitis (2) amyloid (3) tumors of the liver including malignant growths, hydatids, and enlarged gallbladder (4) hepatic suppurations and abscesses (5) symptoms suggesting cholelithiasis (6) imitations of chronic splenic anemia, and (7) cases suggesting hypertrophic biliary cirrhosis. The extension of knowledge has, of course, brought syphilitic hepatic cirrhosis to the front at the expense of other types. Amyloid, in our experience at least as a demonstrable clinical entity is of minor importance. In only 1 case did the behavior of the kidney suggest its presence We have not seen a case of syphilitic abscess of the liver and know of no clinical differential criterion other than the serological reactions and other evidence of syphilis, in a febrile patient with a nodular irregular or lobulated liver evidently the seat

of gummatous changes. Suppurative cholangitis may be deceptive if the patient has coincident syphilis, and must be surgically explored if the patient's condition is at all serious, in preference to attempting a therapeutic test. There remain, then, of Rolleston's group, the misinterpretation of tumors, mistaken diagnoses of cholelithiasis, splenic anemia, and perihepatitis, as the chief sources of diagnostic error linking the older syphilology with the new.

Figure 650 summarizes the material contained in the histories of our patients.

The diagnosis (elsewhere) prior to entering the Mayo Clinic is based on letters of introduction, and the patient's statements, and covers 37 cases. It cannot pretend to represent the actual achievement of the physician at large in the diagnosis of syphilis of the liver inasmuch as patients whose conditions have been correctly diagnosed seldom predominate in the Mayo Clinic. On the other hand, the proportion of correct diagnoses seems rather low even for special circumstances, and the almost wholesale overlooking of syphilis among the patient's ailments is much in point. By the "overlooking" of syphilis, we mean, for example, that patient who has large nodular

Fig. 650

DIAGNOSTIC ERROR IN SYPHILIS OF THE LIVER

Based on study of 73 cases.

Diagnosis.	On referral per cent.	Preliminary per cent.	Final per cent.	Surgical per cent.	Exploration per cent.	Aggregate per cent.
Correct	9	52	63	18	50	47
Partial (syphilis minimized or overlooked)	18	5	8.5	24		7
Indeterminate	9	5	12.5	12		10
Incorrect	64	38	16	46	50	36
Total syphilis overlooked	82	43	24	70		43

liver and symptoms of gallstones may receive a diagnosis of gallstones, confirmed on exploration, but the multiple gummas and lobulated liver then identified, escaped the diagnostician entirely.

Several important points should be recalled in connection with Fig. 650. Some of the cases included date back to a first examination in 1911 when the blood Wassermann reaction was anything but routine feature of medical practice although available in these cases. Many of the cases fall in the era when Wassermann tests, while available, were little utilized. Precise data on the employment of the blood Wassermann test with negative results by physicians elsewhere are not available, except in 1 case, in which three ordinary blood Wassermann tests were negative but the Kolmer technic, used after the patient entered the clinic, gave two strong positive results. In fairness to surgical diagnosis, it should be pointed out that the surgeon is not called to see the large proportion of patients in whom he quite as well as the medical consultant, could make diagnosis of syphilis of the liver on sight. He is merely called to see patients whose surgical complications are suspected by the medical man, who is supposed to have satisfied himself before calling surgeon that syphilis is not the cause of the patient's condition. On the other hand, it should give the surgeon pause to find that he has overlooked syphilis in so high proportion of cases as 70 per cent, and has an incorrect preoperative diagnosis in cases of syphilis of the liver averaging 46 per cent. Some of the errors are avoidable, especially if the surgeon will raise his index of suspicion. By 50 per cent correct explorations (in a total of 16 performed) is meant that surgically treatable condition was found in half the explorations advised (6 of biliary tract lesions and 2 splenomegalies). The 50 per cent of "incorrect" explorations yielded such

findings as are illustrated in the case summaries; gummatous livers with no signs of the expected lesion of the gallbladder; gallbladders bound down by the adhesions of perihepatitis obviously of gummatous origin, active hepatic cirrhoses of the syphilitic type; supposed malignant metastatic lesions which proved to be gummas; and pancreatic and mesenteric tumors which likewise proved to be hepatic gummas, especially of the left lobe. The aggregate accuracy of diagnosis is based on the entire series, and represents the result for the patient so far as could be ascertained, of examination by home physician, clinic medical examiner medical consultant, and surgeon, when called. The average is, of course, lower than that of medical consultants, because single known error on the part of any of the group of four puts the patient in the debit column. In way the result suggests that he who invites difference of opinion among several is less fortunate than he who is able to rely on the comprehensive work-up of one expert, such as the medical consultant.

Causes of Diagnostic Error.—Failure to make a blood serologic test, or properly to interpret it, stands as the overwhelming cause of diagnostic error (Figs. 651–653) The positive blood Wassermann reaction points to syphilis and, while it should not be uncritically accepted as explaining everything in the case (an uncritical acceptance is illustrated in Fig 671) the profession at large cannot afford to substitute its imperfect physical diagnostic acumen for this readily available protection against certain blunders in cases of upper abdominal lesions. In particular the syphilologist and the medical consultant

Failure properly to use the Wassermann
Physical findings deceptive
Supposed gallbladder symptoms
Supposed renal symptoms or signs
Malignancy suspected
Gastric ulcer diagnosed not found
Gastro-intestinal ray omitted lared
Miscellaneous

FIG 641 —PRINCIPAL SOURCES OF ERRONEOUS DIAGNOSIS IN 37 CASES OF HEPATIC SYPHILIS.

should insist that the protection of patient and surgeon from mistakes involving syphilis requires the performance routinely of a blood serologic test and reasonably careful attention to a history of syphilis in every patient who is considered for an abdominal operation. This series of cases includes 8 (21.5 per cent) of diagnostic errors, in which a Wassermann test before operation might have prevented error and 2 cases in which clear-cut histories of syphilis were overlooked until the operative findings led to further questioning.

Deceptive Physical Findings.—These (Fig. 653) are of much importance in the correct diagnosis of syphilis of the liver being factors in error to the extent of 60 per cent. It is only necessary to review the older literature to realize the immense burden of palpatory diagnosis that has been lifted from the shoulders of the physician in his effort to identify syphilis of the liver among the many possibilities suggested by the "feel." The details in the series of cases include

The mere occurrence of a mass or tenderness in the region of the gallbladder does not, of course, eliminate syphilis or justify the omission of the serologic tests. It is entirely possible for a gumma to be indistinguishable from a gallbladder and even for a cystic or enlarged gallbladder to be the product of retention, due to the adhesions of perihepatitis or enlarged nodes in the portal

specific perihepatitis or hepatitis is a puzzling question. From repeated observation of such cases, we are inclined to extend the maxim of Rolleston to the present day and to say that a patient with syphilis who has symptoms of gallbladder disease should not be operated on except in acute emergency until he has had at least one and better two courses of treatment for syphilis, and not merely a preparatory treatment or two. If symptoms recur after the patient is under complete treatment control, operation may of course be indicated, though even then only syphilis may be found.

Symptoms and Signs Suggestive of Lesions of the Kidney.—These served as a source of error in 7 cases (20 per cent) of the series. The attacks of pain in cases of gummatous hepatitis may occasionally suggest the seizures of renal colic (2 cases). The chief source of diagnostic perplexity, however, arises from the position of the gummatous tumor, or the greatly enlarged right lobe of the liver.

If the gummas are large, and obliterate the contour of the liver margin, a lobulated tumor markedly suggestive of polycystic kidney is produced (Fig. 672). The weight of the gummatous mass may be so great as to produce prolapse to the iliac crest, so that it is almost possible to get above the mass by palpation, or at least to believe it entirely below and free from the liver, and hence probably renal in origin. Gummas of the left lobe may produce excellent imitations of a prolapsed left kidney clearly distinguishable from the spleen, if it is enlarged. The possibility of diagnosing an abnormal kidney is increased by functional changes, such as occurred in a case examined by Braasch (Fig. 672) in which the right kidney had twice the functional capacity of the left, with evidence of slight infection on the right. The mass on the right was subsequently proved by treatment to be a gummatous liver, and the suggested left kidney turned out to be the spleen. A marked nephritis with ascites and edema may cover the underlying gummatous hepatitis and splenitis, and only when the renal condition improves under treatment for nephritis may the relaxed, but still fluid-containing abdomen permit a palpatory diagnosis to be made. We are opposed to the tapping of patients with hepatogenous ascites, and so do not recommend paracentesis as an aid to the differentiation of nephritic from cirrhotic ascites. In the nephrosis associated with amyloid degeneration, the large amyloid liver or spleen may be identified, but we know of no way, except by therapeutic test, to identify an amyloid degeneration associated with syphilis. The amyloid kidney retains its function, and the blood urea, water output, and phenolsulphonephthalein excretion remain within normal limits, in spite of the high albumin content. In the one case in which amyloid kidney was suspected, recovery took place in the course of three years, coincident with the return of liver and spleen to practically normal size.

Miscellaneous Sources of Error.—A variety of other diagnostic problems associated with syphilis of the liver presented themselves less conspicuously in the series as follows:

Confusion with Malignancy.—The importance of a routine examination of the stomach by roentgen-ray and test meal in disease of the liver needs no emphasis. To make a clinical diagnosis of metastatic cancer without it is obviously impossible, for the achlorhydria so common in syphilis may not be distinguishable from that of cancer, and left-sided epigastric tumor does not necessarily come from the stomach. On the other hand, in one of our cases an enormous liver supposed to be syphilitic in a patient whose Wassermann reaction was positive and who had neurosyphilis, was found to be carcinomatous, from a primary adenocarcinoma in the stomach, although the roentgenogram was reported negative (Fig. 671). It is important, in connection with the question of malignancy, to emphasize the unwisdom of making merely gross examinations of the abdominal viscera during explorations. A liver studded with nodules may be gummatous, not malignant, as was found in Figure 670, in which the surgeon, even when confronted with a pathologic report of fibrous and necrotic inflammatory tissue from an excised nodule, found it impossible to accept the finding as excluding malignancy, and roentgen-ray treatment was given without result; the patient recovered subsequently under treatment for syphilis. Surgical descriptions of undoubted gummas indicate a wide range in gross appearance in the living patient, from merely flesh tumors indistinguishable from liver tissue to the pale nodular infiltrates of the more superficial or older lesions. Another fact of great importance in connection with the question

of malignancy is that it cannot be eliminated simply by short therapeutic test. Observation over a period of two years or more is often necessary before one can be fully satisfied of the correctness and exclusive character of diagnosis of syphilis of the liver The liver should be carefully watched during treatment; the appearance of definite new masses, especially elsewhere in the abdomen, strongly supports malignancy even in the face of clinical improvement, although it does not prove it. This consideration occasionally justifies exploration before treatment is begun, in order to relieve the patient of uncertainty but we are inclined to believe that this sort of exploration should not be made routinely disregarding the risks of laparotomy

Other Errors.—An important possibility of confusion with duodenal ulcer in cases in which there is hemorrhage into the gastro-intestinal tract exists. In one such case in which the spleen could not be felt, owing to adhesions, the roentgen-ray findings were those of duodenal ulcer which could not be found t operation (Fig. 674). In another case the nocturnal backache, with epigastric pain and gastric symptoms, suggested duodenal ulcer clinically but the roentgen-ray findings were negative. It is, indeed, surprising that this error was not more common, since it is easily understandable. Tenderness at McBurney point and symptoms typical of appendicitis occur but, from the frequency with which chronic appendicitis is found at exploration, we are inclined to believe that the appendiceal symptoms are coincidental, and not part of liver syndrome due to syphilis. Right-sided pleurisy was the first diagnosis in 2 cases (Fig. 666),

Fig. 653.

MISCELLANEOUS MINOR CAUSES OF ERROR IN DIAGNOSING HEPATIC SYPHILIS BASED ON A STUDY OF 73 CASES

	Cases.
Malignancy was Suspected in 5 Cases, Including	
Cancer of the stomach not present	2
Cancer of the gall-bladder and ducts not present	1
Metastatic carcinoma not present	1
[illegible]	1
[illegible]	4
[illegible]	4
[illegible]	2
[illegible]	2
Appe[illegible]	2
Pleurisy (right sided)	2
Tuberculous Peritonitis	1
Surgeon Trusted Gross Appearances on Exploration (made diagnosis of malignancy hen not present)	2
Complaint Thought to be Cardiac (supposed anginal attacks)	1
Hasty Surgery	1

evidently an expression of perihepatitis on the lateral surface of the right lobe of the liver It was followed later by typical hepatic symptoms. It is matter of some surprise to us that tuberculous peritonitis was not more frequently confused with syphilitic hepatitis, especially in patients with ascites. The absence of diarrhea in cases of syphilitic hepatitis (though sometimes present in pancreatitis), and the doughy masses of adherent gut and glands assist in distinguishing the late cases. The stools should be examined for fat and for tubercle bacilli.

One patient in the series illustrated a very trying possibility of error the confusion of the attacks of pain in cases of syphilis of the liver with anginal seizures. Hepatic attacks are seldom short enough for the average anginal picture, but they may be agonizing and radiate up into the chest, and even to the left arm, if the left lobe is involved. It is important in all suspected diseases of the liver due to syphilis to roentgen-ray the thorax and abdomen for aneurysmal dilatation of the aorta; this occurred in one of the cases, and was an important element in symptoms and prognosis.

Attacks of gastric crisis in tabes dorsalis, if associated with enlargement of the liver may provide most puzzling picture, as attested by the number of patients with crises who have upper abdominal scars, although this group contains no cases in point. (See Chapter XX.) The recognition of the tabetic type of neurosyphilis, the prominence of gastric symptoms as compared ith hepatic, the obstinate and conspicuous vomiting element, and the superficial or skin

tenderness, as contrasted with the deep soreness of the syphilitic hepatic or gallbladder attack, serve to distinguish most cases. The liver subsides promptly under treatment, although the crises recur periodically for a much longer time.

To summarize the outstanding points, then, the routine use of the serologic tests may be urged on all physicians as an aid in the interpretation of abdominal lesions with reference to the syphilitic liver. In our experience, at least, there is more danger of its underuse than its overuse, although uncritical interpretation of the findings in patients with positive serologic reactions is *always to be avoided. There is a serologic negative syphilis of the liver* but it is, so far as our present experience goes, uncommon. The average diagnostician should accustom himself to think of syphilis as able to reproduce every feature of biliary tract and hepatic disease, and to raise his threshold of suspicion to the point where he can cope with it. The more reliance he places on physical findings and history, as contrasted with serology and therapeutic test, the larger, in all probability, will be his error with respect to syphilitic hepatitis.

THE TREATMENT OF SYPHILIS OF THE LIVER AND SPLEEN

Modern methods, instead of simplifying the problem of treatment of syphilis of the liver, have increased its complexity, albeit, with proper application of fundamental principles, these methods have likewise improved the outlook of the patient for a permanent result and restoration *to functional* normality. The successful treatment of hepatic syphilis is a problem as special as the treatment of syphilis of the cardiovascular system, and much more difficult than the management of gastric syphilis.

The Rationale of Treatment.—Certain general considerations must be constantly kept in mind in the management of hepatic syphilis. In the first place, the liver is sensitive to heavy metals, and in any system of treatment in which arsenic plays an important part, it may be expected to sustain a certain amount of damage, which may or may not lead to embarrassing complications. In the second place, both liver and spleen are storage depots for arsenic and they act as accumulators of the drug whenever arsphenamines are used, whether in the treatment of general syphilis or of syphilis of the liver and spleen as such. It is to be expected, therefore, that the structurally damaged liver and spleen will have a reduced storage capacity and show symptoms of irritation earlier than the normal organs whose parenchymatous reserve has not been cut down by disease. They will likewise presumably throw a heavier burden on other structures in which the drug may accumulate, such as the skin. In the third place, fortunately for patient and therapist, the liver especially has a large parenchymatous reserve, and much of its substance can be replaced by gummatous infiltration or fibrous scar *with good recovery*. In the fourth place, the liver contains a vulnerable vascular mechanism in the form of the portal system, which must be kept intact as far as possible. If this mechanism is too extensively damaged, the influence on the general nutrition of the patient is such that while he might survive his mechanical defect, he cannot survive it in combination with undernutrition and damaged metabolism. Mechanically, blockage of the portal system, whether of its capillary branches by diffuse fibrosis, or of its larger radicals by pressure from gummas, or distortion by scar contraction, must be compensated for. Out of the foregoing considerations arises the fifth point, that the liver must be protected in every possible way, as must the myocardium, from the effects of fibrosis, whether due to the slow inflammatory processes of the disease, or the effects of rapid scarring by intensive treatment.

The Hepatosplenic Therapeutic Shock.—The liver and spleen are among the ideal sites for the Herxheimer reaction and the therapeutic paradox. They are favorite locations for *Spirochaeta pallida* and show, therefore, a pronounced flare-up in spirillicidal methods of treatment when large doses are employed at the outset. In the case of the spleen the therapeutic shock is of little consequence. *In the liver, however, the effects of a severe Herxheimer flare-up* may be prolonged and serious, and even precipitate a toxic reaction that may be fatal. Since the liver and spleen

are storage depots for spirochetes as well as arsenic, it should follow that incomplete destruction of the organisms by treatment will result in a correspondingly rapid and serious relapse. The exact status of this hepatorecurrence on which the French writers and especially Milian have laid so much stress, is not as yet worked out, but it undoubtedly exists, and may be the explanation of certain supposed toxic jaundices from arsphenamine. It follows, therefore, that any treatment of the liver for syphilis must be carried through to prevent relapse and a state of affairs worse than at the outset. Several cases in this series illustrate this point.

Therapeutic Paradox.—The therapeutic paradox in syphilis of the liver differs in no essential particular, so far as its mechanism is concerned, from that in the cardiovascular system. In the spleen, because of its relative unimportance the therapeutic paradox is usually of small moment. The presumption is that the earlier in the course of syphilis involvement of the liver can be detected, the better the outlook for escaping the therapeutic paradox. This most important consideration calls again for an increasing application of the routine serologic test to all patients, and special regard on the part of the physician for the possibility of syphilis in those of his patients who present palpable livers and spleens. Figure 657 is an excellent example of the penalties which the patient must pay for the failure of the clinician to appreciate the import of an enlarged liver. Escape from therapeutic paradox by way of the older less intensive method of treatment is not as simple as it seems at times. Another patient was recognized as having syphilis of the liver in 1911. Six years of mixed treatment by mouth, while it retarded the course of her disease, in all probability failed to produce a curative result, and in 1917 she was seen again with an advanced aortitis, the liver about as large as formerly but evidently now cirrhotic, and an ascites of extreme grade associated with a nephrosis. Treatment for syphilis of the liver, moreover, while taking account of the peculiarities of the structure mainly involved, should, none the less, be also effective treatment for syphilis, and should not, while holding a relatively benign process in check, permit

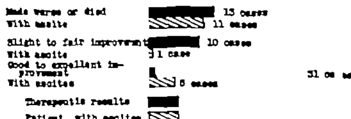


Fig. 656.—Therapeutic Results in 45 Patients with Ascites.

the development of a grave syphilitic complication such as aortitis. This is, of course, not a reflection on the management of cases seen in the first decade of this century when arsphenamine, if it had been applied at all, would probably have brought about disaster through relapse.

The three types of hepatic and splenic lesions with which one is called on to deal in syphilis require different types of therapeutic management. Early syphilis of the liver and spleen is an acute parenchymatous inflammation, recovering easily under ordinary treatment in most cases and leaving few or no residua, but prone to relapse (Fig. 641) if not sufficiently treated, and disposed to sharp reaction if given a severe therapeutic shock (Fig. 676). Late syphilis of the liver usually combines two types of lesion, the local gumma and the diffuse infiltration, which have radically different prognoses under treatment. The solitary gumma resolves readily under any intelligent management, seldom leaving a scar which has any ill effects, and often healing spontaneously even to the resolution of the perihepatitis and adhesions over the involved surface. Relief from pressure phenomena and the secondary effects of peritonitis, including transient jaundice and ascites, is usually prompt and there are no late by-effects. On the other hand, general damage to the liver with extensive fibrosis is the earmark of cirrhotic hepatitis and of those cases in which the cirrhotic phase is uppermost. Intensive treatment in such patients gives rise within a short time, varying from a few days to several months, to the therapeutic paradox (Fig. 677). Herxheimer reactions, with transient swelling and further obstruction in these seriously damaged livers, are often grave, and it is the usual thing for the patient to get distinctly worse, especially as regards ascites and jaundice if present, during the first few weeks of almost any treatment regimen. The rest period in which the patient reestablishes his functional equilibrium becomes, at times, more important than the treatment phase of his management.

It is apparent, then, that one of the most important questions the therapist is called on to answer when he assumes charge of a patient with syphilis of the liver concerns the relative proportion of localized gumma formation, and of diffuse inflammatory infiltration which the given

case presents. It is rarely possible to answer this question with the satisfying definiteness that would make one feel safe in boldly giving a patient with pure gumma liberal doses of arsphenamine, while giving a long iodide course to the cirrhotic patient. The processes are usually so intermingled that some disagreeable surprises inevitably await the overenergetic therapist. Inasmuch as prognosis is involved in the decision there are, however, certain guides which assist in determining the outlook. The age of the infection is, of course, of value in "latent livers," but untrustworthy in fully established cases. Intermittent symptoms and a stormy course of chills, fever, and the accompaniments of localized perihepatitis suggest gumma rather than cirrhosis, and these patients usually tolerate the more vigorous treatment and rapid approach (Fig. 661). Insidious onset, with fluid accumulation as the first sign, and gradually progressive distention, point to cirrhosis. The presence of ascites, then, is a distinctly unfavorable feature in the aggregate, and a definite warning to proceed slowly, although there may be exceptions due to obstructive action of gummas, enlarged glands, or perihepatitis in the portal fissure. Patients with syphilis of the liver with abdominal fluid require the most skillful management, and can seldom be promised the best results unless they can devote weeks and even months to proper preparation and to the establishment of their compensatory mechanism. Figure 656 illustrates the difference in prognosis of patients with ascites, as compared with the aggregate.

The physical characteristics of the lesion of the liver are of some assistance in deciding on the type of treatment, although by no means always trustworthy. The sharply defined, rapidly developing tumor with acute symptoms is usually a gumma, and if the antecedent process is not of too long duration, the patient will probably require less preparation than the patient with the cirrhotic type of disease. Diffuse enlargement of the liver, late in the disease, with few symptoms, should be thought of as probably fibrotic, the size or consistency of the liver not being trustworthy as a decisive point between acute diffuse gummatous hepatitis and old cirrhosis. *Hepar lobatum* is not always amenable to vigorous treatment. The damage to such a liver may also be diffuse, and its further distortion by rapid healing of multiple gummatous foci may bring on a therapeutic paradox.

While pathologists may hesitate to accept the instrumentality of alcoholism in the production of hepatic cirrhosis, my experience at least indicates that the fate of the drinker with hepatic syphilis is distinctly less favorable (Fig. 656) than that of the nondrinker. The prognostic relation corresponds quite closely to the relation between alcoholism and the incidence of ascites as previously shown.

Treatment of Early Acute Hepatitis.—The advent of bismuth has simplified the situation here, making it possible to treat these patients vigorously and at the same time fairly effectively so far as response of surface infectious lesions if present is concerned, until the return of the icterus index to normal as in Elliott and Todd's case. Personally we believe it entirely safe at this point to resume or institute the use of an arsenical in moderate doses in the effort to secure a curative effect in early syphilis.

Grave icterus should be watched for in all patients with syphilis who present jaundice early, as well as in others in whom it may occur without warning, for an early diagnosis is essential if the patient is to be saved. Here again, bismuth, vigorously employed, may be expected to be superior to mercury, the first choice in the past, and preferable to the theoretically objectionable arsphenamine. Wile's case responded to calomel intramuscularly and iodide by mouth. Some of the problems which a grave icterus may present are well illustrated by Fig. 676.

Etiologic Differentiation and Treatment of Various Types of Jaundice.—The decision of the syphilotherapist as to whether he is dealing with a toxic icterus from arsphenamine, a syphilitic icterus, an intercurrent infectious, catarrhal jaundice, a hepatorecurrence following inadequate previous treatment, or an icterus associated with gallstones or cholecystitis, is often important and beset with many difficulties.

Acute toxic icterus usually comes on in fulminating fashion, often in association with an exfoliative dermatitis during an arsphenamine course. If very low dosages of arsphenamine

have been used, it is perhaps permissible to suspect hepatorecurrence at this time, but, as rule, the hepatorecurrence is an interval manifestation, begins between courses, and comes on while the patient is on mercurials or iodide, or during rest period. It is, therefore, particularly confusable with the so-called "late arsphenamine icterus" which has usurped so much attention since the war This complication, in turn, at the present time at least is inextricably interwoven with a form of catarrhal infectious jaundice which has been responsible for an epidemic that has covered the entire world in sporadic outbreaks during the last fifteen years.

Infectious epidemic catarrhal jaundice is in our experience is the commonest hepatic disturbance encountered in treating syphilis at the present day T ose having any considerable experience with it, the prodromes become so easily recognizable that it is possible to predict, often as much as month in advance, that patient will have jaundice. Urticaria and arthritic pains, often of great severity are quite common, and may last for week or two, with gradually increasing anorexia, discomfort in the epigastrium or right upper quadrant, and loss of weight, before jaundice ppears. The liver is usually large, the jaundice moderate, the urine bile-stained, the stool acholic. In severe cases the loss of weight may be rapid, the jaundice deepens, and if the liver begins to shrink and toxic delirium sets in, death from acute yellow atrophy impends. Treatment for syphilis has no effect on the process, thus eliminating hepatorecurrence. There is usually no arsenic found in the urine, nor was there any in the liver of several reported cases coming to necropsy The gradual onset and obstructive signs have led to explorations for common duct stone, but with no other findings than those of cholangitis. True gallstone attacks are usually more acute in onset and short in duration. Edema of the papilla of Vater associated with duodenitis is suggested in some cases. In one of our cases at necropsy pus was found in the ampulla and common duct and there were signs of duodenitis. Relapse may occasionally be noted irrespective of treatment for syphilis. In the more prolonged cases ascites may develop and evidence of considerable though temporary functional impairment of the liver be found. Edema of the legs without detectable ascites is pending manifestation in some cases, but usually responds to bandaging and rest. The verage duration in number of cases observed by us was from thirty-five to forty-five days.

Differential Summary of Jaundice in Syphilis.—The average physician confronted with the duty of deciding just what he is dealing with when a patient with syphilis appears with jaundice may adopt the following course of reasoning suggested by the parallel column analysis of Fig 657 If arsphenamine has been given within a week or two, and there are signs of itching skin and beginning dermatitis, sodium thiosulphate intravenously may be employed in doses of from 0 5 to 1 Gm. every other day for several doses, and the effect watched. Glucose intravenously and similar measures are described in Chapter IX. The condition is probably an arsphenamine toxic jaundice, and the patient is likely to develop an exfoliative reaction. If the patient has not been treated for syphilis, the condition is more likely to be syphilitic, and a decision must be made as to whether the process is early or late. If it is early (patient with a secondary eruption or its residua) treatment with neoarsphenamine may be begun after a week of mercurial preparation with the succinimide or bichloride or bismuth may be used from the start. On the other hand, if the infection is not recent, all the factors which enter into the diagnosis of hepatic injury must be considered and painstakingly eliminated If the decision is in favor of syphilis as the cause, treatment should be begun as will presently be described under late hepatitis. If the patient has had treatment for syphilis in the past few weeks, months, or years, it should not be too readily concluded that he is suffering from a toxic arsphenamine icterus. He should be placed on the regimen for epidemic infectious jaundice, his symptoms from the right hypochondrium should be interpreted with reserve, and operation should be resorted to only after two or three months of persistent jaundice has failed to respond to the catarrhal regimen, or to later treatment for syphilis. In fact, several experiences suggest that it is a serious matter to explore these epidemic cases, and that a fatality may be precipitated in this way

Fig. 637

A DIFFERENTIAL SUMMARY OF JAUNDICE AND HEPATITIS IN THE SYPHILITIC PATIENT

Early acute syphilitic hepatitis (benign)	Acute yellow atrophy	Hepatorecurrence.	Acute arsenical hepatitis.	Infectious catarrhal jaundice.	Late hepatitis (cirrhotic and gummatous)
Rare	Rarest.	Probably not uncommon.	Uncommon.	Probably commonest form.	Uncommon.
Occurs primary or secondary stage only	Occurs in primary or secondary stage.	Occurs in previously inadequately treated early and latent cases.	Occurs in previously treated patients at any stage, not necessarily overtreated.	Occurs in previously treated or untreated, or even in nonsyphilitic patients.	
	Rapid onset.	Onset weeks or months after lapse.		Onset during or even long after treatment.	
Severe jaundice	Severe jaundice.	Jaundice variable, usually marked.		Jaundice usually gradually progressive in onset, mild or deep.	Jaundice often insidious or fluctuating over months or years.
Liver enlarged and tender	Liver large, then small.	Liver usually enlarged.	Other concomitants of arsenical poisoning, especially dermatitis, aplastic anemia, hemorrhages, polyneuritis.	Liver variable.	Liver if palpable may show masses or lobulation.
Spleen seldom palpable	Great prostration. Diarrhea, foul stools. Spleen rarely palpable.	Symptoms resemble early acute hepatitis.		Onset insidious, 2-4 weeks prodrome of arthralgia, urticaria and gastro-intestinal symptoms.	Subjective symptoms mild and insidious, with cirrhosis; stormy (pain, fever etc.) with gumma.
Few other symptoms except those usual in jaundice (depression, itch, gastric disturbance, slow pulse)	Toxic delirium. Fluid in abdomen.	May go over rapidly to acute yellow atrophy. No response to duodenal drainage.	No response to bismuth or mercury unless made worse (nephrosis especially)	Often part of an epidemic.	Palpable spleen 50 per cent. Fluid may be present.
Hypo or acholic stools.	Rapid course to fatal outcome (4-5 days).	Rapid response to further vigorous treatment with arsphenamine or bismuth.	Symptoms of acute yellow atrophy often ensue.	May go over to acute yellow atrophy or with sudden onset as such.	Hematemesis and melena in cirrhosis.
Urine, bile only	Urine may contain casts, tyrosin, leucin crystals		Nephrosis may be present.	Marked weight loss.	Weight retained until late.
Variable weight loss.					

Fig. 657 (Continued)

A DIFFERENTIAL SUMMARY OF JAUNDICE AND HEPATITIS IN THE SYPHILITIC PATIENT (Continued)

Early acute syphilitic hepatitis (benign).	Acut yellow atrophy	Hepatorecurrence.	Acute arsenical hepatitis.	Infectious catarrhal jaundice.	Late hepatitis (cirrhotic and gummatous)
Icterus index variable, too high.					
N previous arsphenamine treatment.			Arsenic strictly contraindicated.	Arsenicals tolerated in moderate doses.	Arsenicals may give quick improvement, but paradoxic result.
Quick response to bismuth therapeutic test (2–3 weeks).	Bismuth or calomel intramuscularly may be tried, but mortality is high.		Response if at all to sodium thiosulphate and other detoxifying measures.	No response to treatment for syphilis.	
N response to duodenal drainage.				Quick response to duodenal drainage.	No duodenal drainage response.

Fulminating jaundice with toxic symptoms should be carefully searched for evidences of recent syphilitic infection since, if they can be found, the outlook by intensive treatment for syphilis is quite good, although absolutely nil without it. Other forms of acute yellow atrophy do not respond. The possibility of an early toxic pregnancy must be kept in mind in women

Treatment of Late Syphilitic Hepatitis.—It is easy to reap disaster from a too hasty or too energetic therapeutic approach in late syphilitic hepatitis. The therapist should give due heed to the art of therapeutic coddling, and restrain his desire for arsenical miracles. If there is any sign of fluid, or the case is of long standing and of insidious onset, it is well to ask for hospitalization and a period of two or three months of cautious treatment for the first course

First week or two, potassium iodide by mouth, 1 to 2 Gm. three times daily if tolerated, and mercury with chalk, 1 or 2 grains three times daily

Second to fourth week, inunctions in addition, 4 Gm., 30 grains, clean. During this period iodide may be given intravenously if the patient's condition is good or his gastro-intestinal tolerance poor As a rule however 30 grains three times daily by mouth is sufficient. The dose intravenously should be 3 to 8 Gm daily or every other day

Fourth to sixth week, if progress is slow and there are no unfavorable signs from the kidneys, succinimide intramuscularly or the bichloride may be substituted for other mercurialization, the iodide being continued.

The Use and Dangers of the Arsenicals in Late Hepatic and Splenic Syphilis.—The undoubted gravity of the therapeutic paradox and the very natural fear of using a hepatotoxic drug in a patient with a damaged liver have combined to produce a fundamental distrust, if not an absolute prohibition, of the use of the arsphenamines in late syphilis of the liver and spleen. With this point of view we are, in the main, in sympathy and our caution has only grown with experience O'Leary in surveying the proved hepatic syphilis of the Mayo Clinic in 1931 gave this question special consideration and came to the conclusion that the prognosis of patients receiving only mercury and iodide was definitely better than that of those also receiving arsphenamine. In late forms of hepatic syphilis the continued use of mercury and iodides at intermittent intervals for several years has resulted in an average life expectancy of almost three times that when arsphenamine and mercury were used intensively There is no reason to expect that mapharsen will improve the record of the arsphenamines for therapeutic shock effects. McCrae has been unsparing in his condemnation of the use of the arsphenamines and his preference for mercury and iodide in syphilis of the liver We have seen a therapeutic paradox develop in a prenatal syphilis on our own service which had apparently sustained what we at the time regarded as adequate mercurial preparation, though applied to the wrong type of case We are convinced that it is out of the question to expect of the majority of physicians called upon to treat syphilis of the liver the necessary discrimination to enable them to avoid the dangers of arsphenamine therapy For this reason we no longer allow our medical students to consider its use nor do we advocate it for the practitioner Pending the determination of the suitability of bismuth in the treatment of hepatic syphilis (and we believe it to be subject to many of the objections which apply to the arsphenamines) we recommend that all patients with late hepatic syphilis be treated with mercury and iodide.

It is impossible however to escape the fact that a very considerable pro-

portion of patients with syphilis of the liver especially of the noncirrhotic types, do extremely well on the arsphenamines. We have seen operative confirmation of the inability of mercury and iodide by ordinary methods of administration to hold some cases of progressive hepatic syphilis in check. Korns, in his critical examination of the problem of syphilitic Banti's disease, directs attention to the fact, with which our own limited experience is in accord, that a great many of the reported cases of syphilitic Banti's disease with extensive changes in the liver as well as the spleen, have done exceedingly well on one or another of the arsphenamines, as evidenced by half a dozen reports in the literature. We believe, therefore, that the exclusive use of mercury and iodide should constitute the recommended treatment for syphilitic hepatitis in all its later stages, but that given a sufficiently expert selection of the type of case, sufficient heavy metal and iodide preparation, and sufficient judgment and skill exercised in the selection and dosage of the arsphenamine employed the arsenical group of drugs may have a definite place in the management of noncirrhotic types of patients who are still in the early stages of the disease and free from any suggestion of portal obstruction or serious hepatic dysfunction. For the practitioner and the internist, we do not recommend it.

Bismuth in Hepatic Syphilis.—The ability of bismuth to produce Herxheimer effects in acute processes and the possession of definite hepatotoxic properties by the drug, is well recognized. For these reasons, if bismuth employed in the treatment of hepatic syphilis (and it may be said that as yet no clearly defined technic has been worked out) the dosage should be moderate at the start or small with short intervals or especially in the late and cirrhotic cases, the drug should only be used if mercury and iodide fail of effect, or if there is a high degree of anemia or marked nephrosis. Bismuth may like an arsphenamine, be used after prolonged mercury and iodide preparation if there are no apparent contraindications.

Subsequent Treatment.—This must depend on the patient's progress. Two or three thoroughgoing courses of mercury inunctions and iodide should be regarded as the minimum. An arsenical, if given, should be in the form of "914" mapharsen or bismuth arsphenamine sulphonate the dosage should be moderate (not higher than 0 45 Gm. "914" or 40 mgm mapharsen respectively) and the courses long rather than short to avoid stimulating a hepatorecurrence. In the recommended form of treatment without arsphenamine, measures to combat anemia may be necessary and the rest periods between inunction courses should be as long as three or four months to allow for the marked response to rest which many of these patients show Iodide, however should be continued throughout the rest period and, if necessary suspended during the inunctions. Patients who improve should be impressed with the great importance of observation and of close attention to their treatment intervals, which their sense of well-being and striking improvement may lead them to overlook. Only in this way can a certain proportion be protected from the development of serious relapse or of other manifestations of syphilis. A follow up system is as necessary in visceral as in early syphilis.

SPECIAL ASPECTS OF TREATMENT

Certain collateral factors appear in the management of patients with late syphilis, including the control of ascites; management in the face of nephritic, cardiovascular, and neurosyphilitic complications; utilization of the rest period; the problem of surgical intervention and treatment, and the performance and interpretation of the therapeutic test.

Control of Ascites.—The slow approach in the treatment of syphilis of the liver is the best preventive of an embarrassing ascites (Fig. 677). When a marked degree of ascites is already present or develops as a transient effect, it is best controlled, not by tapping, but by restriction of fluids by mouth and elimination through bowels and kidneys by catharsis and diuresis. Brisk purgation with concentrated saline can materially relieve distended abdomen and, if the patient's general condition is reasonably good, additional hydragogue catharsis with jalap (1 to 2 grains daily) has proved very satisfactory in our work. Tapping, on the other hand, has its definite dangers, and tends to perpetuate its necessity until the patient is worn out, or until some serious injury such as puncture of the intestine ensues. It should definitely be thought of as a last resort, and not the first measure to be employed when the patient enters hospital, as is too often the case. In persons over fifty years of age, or those who have had marked ascites for some time, the effect of a single tapping, especially if much fluid is removed, may be disastrous. A species of liver crisis, akin perhaps to the pleural crises of patients with effusions of the chest, ensues, diffuse abdominal pain, great prostration, and symptoms suggesting uremia develop with fatal outcome in from a few hours to several days. Stokes has seen 2 deaths from this cause and nothing can more thoroughly impress one with the propriety of relegating paracentesis to the rank of last resort. The condition of the kidney has an important influence on the degree of ascites in a hepatic case, and no relief may be obtained if there be nephrosis present, until the contributory factors to the nephrosis, such as focal infection, are removed. In fact, renal irritation from mercurial treatment appears at times to be responsible for fluid retention, which subsides when change in methods does away with the cause. The use of the mercurial diuretics novasurol and salyrgan has achieved considerable popularity and follows the same principles applicable to their administration in edema and ascites of cardiac origin as described on page 963. Overstrain and heart damage contribute to the ascites of hepatic cases. In one of our patients, previously free from fluid for many months and with no recognizable cardiac lesion, temporary distention followed a severe physical strain of several weeks' duration, but completely subsided under subsequent rest.

Collateral Circulation.—The development of a collateral circulation through the epigastric veins in cases of severe portal obstruction requires in our observation seldom less than two years. Forcing the superficial vascular system to handle its overload by reducing paracentesis to a minimum, seems to be of value and all constricting interference from clothing should be avoided. In patients who have been thrown into therapeutic paradox by too early or intensive employment of arsphenamine, the battle must be fought quadrangularly between catharsis, diuresis, paracentesis, and the maintenance of the patient's nutrition and morale. Small sallies of iodide and mercury with rest periods, are much more effective than continuous pummeling.

Management of Complications.—In patients with coincident nephritis or nephrosis associated with amyloid changes, the treatment of the nephritis must be carried on hand in hand with that for syphilis, iodide being relied on for the preparation, and arsphenamine for the later treatment, and mercury altogether omitted for the time being. Very fair results can be secured in this way. The treatment of cardiovascular syphilis so closely resembles that of hepatic syphilis that there is no conflict. Concomitant neurosyphilis will respond to the same measures, but their intensity should be increased by the later use of neoarsphenamine in 0.45 Gm. doses intravenously and Swift Ellis-Ogilvie intraspinal treatment if warranted by the spinal fluid findings. The liver seems to tolerate tryparsamide well, if there is occasion to use it in a neurosyphilitic patient.

Rest Periods.—The rest period, as we have intimated, is a vital part of the management of difficult cases. It should be made proportional, to some extent, to the depression produced by treatment. In general, not until the patient has rallied entirely from any signs of overtreatment should he take up again the systematic use of mercury or arsphenamine. On the other hand, those patients who improve at once and strikingly should be held to shorter rest periods, and effort be made to suppress their infection entirely with complete and final reversal of the Wassermann reaction. The latter should not, in general, be used as a guide to treatment in the first year or two.

Treatment of Hepatic Syphilis as Liver Disease.—This heading is intended to cover the general medical management of hepatic disease in patients with syphilis. A group of measures often neglected includes the strict prohibition of alcohol, the sharp reduction of fat intake, with increase of protein and carbohydrate in the diet; the supporting of liver function by large doses of vitamin B complex, the promotion of intestinal elimination and the avoidance of intestinal infection wherever possible, and the use of liver extract by mouth or intramuscularly. The good effect of extending such protection to the liver far back in the course of hepatic disease associated with syphilis when liver enlargement is first manifest (see Fig. 641) will probably become more apparent as the physician in charge of the case becomes more preventively minded and foresighted.

Surgical Intervention.—In general, the emphasis on gallbladder symptoms as evidence of surgically treatable disease is so great that it is difficult for the syphilologist to dissuade the surgeon from too immediate intervention. There have been evidences of ill-effect on the patient, of which Fig. 663 is an example. In general, syphilitic patients should be spared all possible resistance-lowering shocks. On the other hand, if, after two or three months of treatment with arsphenamine and mercury the patient sustains relapse of symptoms pointing to gallbladder disease, exploration may be advisable in order to treat the coincident condition, if present. Even under such circumstances, several cases illustrate the fact that relapse in the syphilis, and not concomitant gallstone factor, may be responsible for the recurrent symptoms.

Chapman, Snell and Rowntree (1933) plead strongly for the early surgical exploration for accurate diagnosis and for the consideration of the various operative measures now available to prevent the worst of the late consequences of hepatic cirrhosis. T quote certain of their conclusions, "It is apparent that the alcoholic patient ith an enlarged liver and positive bromsulphalein test has only about an even chance of surviving for three years or more, regardless of the fact that he has not reached the stage at which most clinicians would make an unqualified diagnosis of cirrhosis. It also appears that the patient with chronic or intermittent jaundice and an enlarged liver has an equally unfavorable prognosis. If syphilis is included as an etiologic factor the gravity of the situation may be somewhat decreased. Patients with Banti' disease and secondary cirrhosis who have not yet reached the stage of portal stasis and ascites have a reasonably good outlook. Since, in the whole group, surgical exploration ppears to be well tolerated, perhaps it should be considered more often, especially in view of the possible relation of splenic and cholecystic disease to cirrhosis. No doubt omentopexy or ligation of the venous channels communicating with the esophageal vein as performed by Walters, could be done with greater prospects of benefit in compensated cases. W feel that either history of hemorrhage or the finding of collateral venous circulation may constitute definite surgical indication in compensated cirrhosis of this type. If patients have an alcoholic background and history of



Fig. 672.—Therapeutic Results in Alcoholics and Nonalcoholics.

haematemesis, the question of Talma-Morrison omentopexy and ligation of collateral venous channels connecting with the esophageal plexus should be seriously considered. Excellent clinical results have been obtained by this procedure, and failures have been chiefly due to the very advanced state of the disease at the time of operation. Splenectomy may also be considered in this connection; it is performed too late in many instances, and may offer far more in the latent case of cirrhosis, particularly if there is history of haematemesis and anemia with moderate or low degrees of retention of dye. It is apparent that surgical procedures in these latent or compensated cases should be considered more seriously in the early stage than in the advanced or decompensated stage.

Splenectomy.—The operation is by no means one of negligible mortality even in the hands of an experienced operator and with inexperienced operators may well be more serious matter than the disease. The adhesions often met with due to perisplenitis increase the technical difficulties. Four of the patients in the group here reviewed had sustained splenectomies, and 2 cases, typical of the good results, are shown (Figs. 674 675) One patient died from postoperative hemorrhage. He had been making favorable progress before operation. Another patient received no benefit, although the pathologic picture suggested Banti syndrome; he died later of hepatic cirrhosis. Splenectomy for persistent anemia resulted in permanent increase in hemoglobin of about 10 per cent in third case, and definite improvement in well-being. Where definite indications, such as hemorrhages from varices exist, splenectomy is undoubtedly in order The bleeding may be exaggerated by the effects of treatment for syphilis to the point of being the cause of death. On the other hand, systematic treatment has not had all the trial it deserves in cases of hepatosplenic syphilis. Splenectomy is hardly tonic measure for general application in visceral syphilis The reversal of the Wassermann reaction in cases of syphilitic splenomegaly following removal of the organ, is desirable, but we have been able to obtain it without surgical intervention, and have also noted Wassermann relapses after splenectomy Certainly splenectomy should not be resorted to in hepatosplenic syphilis until treatment has done its best and fallen short.

This means not less than a year of effective arsenical, mercurial and iodide treatment, and of two or three years treatment in a difficult case. When all is said and done, there will remain a few cases in which persisting asthenia and anemia should be attacked by this method after systemic treatment has failed to meet the situation.

Talma-Morison Operation to Control Ascites.—Surgical treatment of persistent ascites includes the so-called "Talma Morison operation of establishing a compensating peritoneal lymphatic drainage by suturing the free border of the omentum to the parietal peritoneum. Riesman called attention to the favorable results that may ensue, and Stokes has seen one example. Riesman remarks on the species of spontaneous or accidental Talma-Morison effect which may follow repeated tappings, in one or several of which the patient may have peritoneal reaction that attaches his omentum to the abdominal wall at the site of successive punctures, with the establishment of an venous of drainage, which in time brings him relief. Chapman et al. just cited advise its earlier use if exploration justifies.

Therapeutic Test for Hepatic Syphilis.—The therapeutic test for syphilis was the court of last resort in differential diagnosis in a much larger proportion of cases in the past than at present, when the serologic reaction has so immeasurably clarified the situation for both patient and physician. On the other hand, it is till a necessity and should be well understood as the logical resolving factor for an indeterminate diagnosis. In lesions of the gallbladder the effect of treatment for syphilis may be immediate, especially if the survey of the case justifies the early use of arsphenamine. Chills, fever and pain usually subside at once, but their recurrence during subsequent mercurial course cannot always be taken as evidence that the process is not syphilitic, and that gallstones are present. Mercury and iodide can produce an effect within two to three weeks. We have seen no evidence of nonspecific action of arsenical on cholelithiasis or nonsyphilitic cholecystitis, recurrence being apparently certain if something other than syphilitic factor is present. In cirrhoses, the tendency of those who are watching therapeutic test is to expect results too soon in difficult cases. Three or four months will be needed to demonstrate favorable reaction, and test should not be adjudged failure simply because the patient is not restored to normality within that time A year and even two years, will often be needed to demonstrate that the patient has recovered from hepatosplenic syphilis with ascites.

In the therapeutic test for cancer the patient usually rapidly declines under treatment. Careful palpation of the liver is important, and if new masses are noted at the end of six weeks of treatment, or if glands can be felt by rectum or otherwise that were not there before, malignant involvement is almost certain. Inasmuch as there is little or nothing to be done for malignant invasion of the liver at the present time, the issue of delay for treatment versus exploration is of less significance medically than in operable conditions, such as suspected cancer of the stomach.

RESULTS OF TREATMENT OBTAINED IN THE MAYO CLINIC SERIES

The principles of treatment here discussed have been worked out largely on a group of 53 patients whose aggregate results are summarized graphically in Fig 659 If so good a prognosis can be established for a group of patients

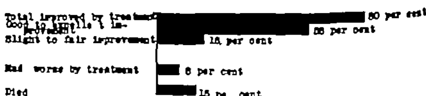


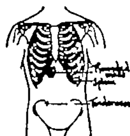
Fig 659 —Aggregate Therapeutic Results in Hepatic Syphilis.

in the pioneering stage, the results obtainable in syphilis of the liver by a *medical profession fully alert to both diagnosis* and treatment should be almost uniformly satisfactory Thirty-eight patients were placed on arsphenamine and mercury simultaneously at the outset of their treatment, without graduated preparation. Of these, 4 patients who developed therapeutic para-

doses were made definitely and permanently worse. This was in the early years of our experience. During this period we also saw several additional examples of the effect of arsphenamine overenthusiasm from outside sources. Since we have appreciated and developed the gradual approach the beginning of treatment with mercury and iodide in 15 cases followed by neoarsphenamine, has led to uniformly good results even in some unusually difficult cases. The mercurial preparation may be made ambulatory by placing the patient on inunctions and iodide for two months or more before arsphenamine is considered. Blood Wassermann reversals are much less difficult to secure than we anticipated. Failure to reverse the Wassermann reaction with routine treat

Fig. 660.

THE "GALL-STONE" ATTACK IN HEPATIC SYPHILIS—PHASE I



Woman, aged thirty-two.

Typical gall-bladder history no preoperative Wassermann taken no syphilis recognized; no gall-bladder pathology found. Syphilitic cirrhosis.

Literal Transcript of Patient's History: "March, 1918, after train trip, carrying 20-pound baby part of the time, noticed soreness below right costal margin; was told she had inflamed gall-bladder. This subsided, but had some soreness off and on since. Last August had two attacks (three weeks apart) of severe stabbing pain under the rib border deep pain, coming in paroxysms all day and associated with deep discomfort below right scapula—some upward pressure. No vomiting, no gas, no bloating. Could not get comfortable in any position. During second attack doctor was called, gave tablets (by mouth) for relief. Was quite sore for several days. No hard attacks since, but since this spring quite uncomfortable with soreness that side. Some indigestion for years—gas and discomfort—slight belching, no selective food distress. Bowels fairly regular. No urinary symptoms."

Note That This is Typical "Gall-bladder" History. The subsequent course was as follows

Physical Examination. Rounded mass which seems to be distended gall-bladder. Spleen palpable. *No Blood Wassermann Test Taken.* No history of syphilis obtained.

Clinical Diagnosis. Chronic Cystic Gall-bladder with Stones.

Operative Findings. Cirrhosis involving entire liver. (Specimen excised, reported cirrhosis.) Stomach, duodenum, pelvis negative. Gall-bladder flaccid and blue. Talma-Morison operation done. Gland from abdominal wall, inflammatory. Chronic appendicitis, moderate grade.

Blood Wassermann Test Taken After Operation. Strong positive. Now found that patient had history of lingual primary and secondaries seven or eight years before, with adenitis. *Lingual scar found.*

ment should lead to a trial of bismuth intramuscularly. Moore's (1923) recent endorsement of the gradual approach with mercury and bismuth from many years experience should be noted. The permanency of the results secured by combined treatment cannot be vouched for as yet, but in some of our most difficult cases the patients have undergone a complete restoration to normal from a condition of the most precarious invalidism. The analysis of the death and morbidity list indicates that the prognosis is even better than the chart indicates, inasmuch as 1 patient in the series died from metastatic cancer of the liver another from hemorrhage and shock following splenectomy 3 suffered relapses from neglect of treatment, 1 died of a liver crisis following para-

centesis, 2 died of cirrhoses in which syphilis was not a proved factor and 1 died of hemorrhages from supposed bleeding duodenal ulcer that did not re-

Fig. 601.

THE "GALL-STONE" ATTACK IN HEPATIC SYPHILIS—PHASE II

Typical gall-bladder attacks; syphilis recognized, but patient explored, no gall-stones; hepatic gumma pressing over gall-bladder: perihepatitis with multiple adhesions.

A Six Year History in man aged thirty-five of ttacks of right subcostal pain with jaundice at times. Duration two hours to three or four days. Soreness between times. Recent severe attack, hypodermic relief. Exercise and lifting bring on attacks.

Physical Examination Tender right subcostal region. No mass. Stomach acids low *x-ray negative, blood Wassermann positive*

Clinical Diagnosis Chronic Cholecystitis 80 Per Cent., Latent Lues.

Operative Findings: There was apparently a gumma the *right lobe* of the liver directly over the gall-bladder, with great many inflammatory adhesions between the dome of the liver and the lateral wall of the abdomen, firmly fixing liver and gall-bladder to the right so that it was impossible even to see the gall-bladder without freeing it, which was not thought advisable. No stones in gall-bladder Appendix, evidence of old trouble. Stomach, duodenum normal.

Postoperative Diagnosis Gumma of the Liver Perihepatitis.

Recovery Under Treatment for Syphilis. Observation eighteen months.

There is N Aspect of the Symptomatology of Gall-bladder Disease, Apparently Which Syphilis Cannot Imitate.

spond to diet, but which in retrospect may have been due to varices associated with splenomegaly and cirrhosis It appears, then that there can be no reason-

Fig. 602.

THE "GALL-STONE" ATTACK IN HEPATIC SYPHILIS—PHASE III

Typical gall-stone and common duct stone ttacks; syphilis recognized and treated, with indifferent results: stones, cirrhosis, perihepatitis all found t operation.

A Woman of Forty-five Became Jaundiced abruptly three months ago. Had had previous ttacks of pain in epigastrium lasting half a day brought on by drinking tea stop suddenly Attacks preceded by chill, sometimes slight fever

Physical Examination Perforated palate, moderate jaundice Mass in right hypochondrium, rounded, descends on respiration. Gall-bladder (?). *Liver palpable*

Blood Wassermann Reaction Positive.

Clinical Diagnosis Treat lues first, though gall-stones probably 75 per cent.

Treatment Inunctions and iodid. Liver reduced in size but patient is still jaundiced and has pain in right side

Operation "Thick walled gall-bladder filled with pus, mucus, and stones. Soft black stony material in common nd hepatic ducts. Liver shows marked cirrhosis with recent perihepatitis. Mild pancreatitis. Stomach and duodenum negative

Postoperative Diagnosis Cholelithiasis, hepatic cirrhosis, perihepatitis.

able ground for therapeutic pessimism in this aspect of visceral syphilis at least.

Fig 663

THE "GALL-STONE" ATTACK IN HEPATIC SYPHILIS—PHASE IV

Typical gall-bladder attacks; syphilis recognized by provocative test. No relief by treatment; operated on after recurrence, gall-stones and cirrhosis found; cholecystectomy; infectious jaundice (?) or hepatorecurrence (?) six months later

A Woman of Forty-nine Had Seven Attacks of right hypochondriac pain, two hours duration, nausea, pale stools, tenderness after attack, jaundice once No chills or fever History of labial primary lesion.

Physical Examination Tender under right costal margin, no masses.

Blood Wassermann Reaction: Negative four positives on provocative (with 3 negatives)

Clinical Diagnosis Gall-stones and syphilis. Treat first and operate if relapse.

Treatment: Three arsphenamin injections. Severe attack following.

Operation: Enlargement regional glands around gall-bladder Gall-bladder contains multiple stones. Liver shows marked hepatitis even to cirrhosis. Pancreas, stomach, duodenum normal Cholecystectomy performed.

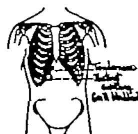
Postoperative Diagnosis Cholelithiasis and hepatic cirrhosis.

Further Treatment with Arsphenamin and Mercury good result.

Jaundice, Severe Five Months Later, with urobilin and urobilinogen in urine. Common duct stone (?) hepatorecurrence (?); infectious catarrhal jaundice (?)

Fig. 664

THE "GALL-STONE" ATTACK IN HEPATIC SYPHILIS—PHASE V



Typical gall-stone attacks with diagnosis of gall-stones. Syphilis recognized. Surgery postponed in favor of treatment for syphilis. Immediate disappearance of all symptoms, with apparent recovery

A Woman of Thirty-seven Stated that she had been told by five physicians that she had gall-stones. She had had six years of attacks of indigestion, with pain radiating under the ribs, residual soreness, sudden onset, and relief Lying on back relieves. Pain radiates lately to shoulder (right). No jaundice or acholic stools. Chills and fever with the attacks and lately at other times. No vomiting

Physical Examination As shown in diagram. "Through-and-through abdominal mass. Stomach, subacidity x-ray negative. Shadow left kidney area. Urine negative. Leukocytes, 10,700.

Clinical Diagnosis Cholelithiasis.

Blood Wassermann Reaction Strongly positive.

Surgical Opinion: Postpone operation in favor of treatment.

Treatment: Six arsphenamin injections, 24 inunctions.

Result Mass Disappeared with Second Arsphenamin. Slight tenderness at costal margin. "Chills and fever" disappeared with first arsphenamin.

Six Months Later: Excellent health, no symptoms.

Husband Examined Also found to have syphilis.

Fig 665

THE "GALL-STONE" ATTACK IN HEPATIC SYPHILIS—PHASE VI

Typical gall-bladder ttacks syphilis recognized, treatment begun, considerable relief mercurial colic and myalgia mistaken for recurrence of ttack in rest period operation for cholecystitis gall-bladder normal but drained unf vorable effect of operation relieved by further treatment.

A Woman of Forty-eight Had Her First Attack of Right Subcostal Pain with Jaundice sixteen years ago. Since then repeated ttacks, with pain radiating to shoulder (right) nd elbow and jaundice N vomiting

Physical Examination Tender Mass, gall-bladder region. Achlorhydria. Jaundice.

Blood Wassermann Reaction Strong positive.

Clinical Diagnosis Probable gall-stones, but possible luetic cirrhosis. Treat before operation if not urgent.

Treatment Six arsphenamin injections, 0 1 to 0.3 gm. Eleven inunctions. Much relief but very intolera t of mercury

Interim Rest and Treatment One month rest, 40 rubs; mouth became very sore, diffuse bdominal cramps, jaundice, salivation, and severe myalgia.

R turns These Symptoms, probably due to mercurial intoxication, ere misinterpreted as gall-bladder syndrome, 90 per cent., and operation done

Operative Findings A very large liver and pancreatitis. The gall-bladder was in pretty good condition, collapsible There ere enlarged glands along the ducts. In iew of the fact that the patient has specific trouble the liver enlargement and pancreatitis are no doubt due to that rather than to cholecystitis. The gall-bladder as opened for exploration Although e would consider it normal, drainage of it may help the hepatitis. Continue antispecific treatment.

Postoperative Course Jaundice became more marked, with increasing pain. Wound healed ell. Liver increasing in size Some ascites. Patient evidently orse Placed on treatment

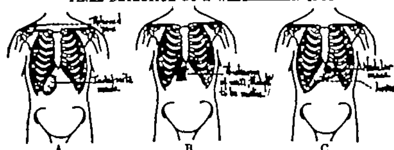
Treatment for Syphilis Ten days small inunction and KI, then neo-arsphenamin 0 2 to 0 6 gm 6 injections.

Result J undice disappears, feels 75 per cent better

Comment This case illustrates the point made in the text as to the length of time needed for therapeutic test. Evidently not all relapses in gall-bladder yndrome in patients ith syphilis are due to gall-stones.

Fig. 886

PROGRESS OF THE HEPATOSPLENIC COMPLEX THROUGH EIGHT YEARS. FINAL DETECTION BY A WASSERMANN TEST



Male, aged thirty

First Diagnosis, 1911, *Pleurisy*. Second Diagnosis (Chart A), 1915, Cystic gall-bladder with stones. *N Wassermann Test.* Operation Performed.

Operative Findings: Thick-walled gall-bladder buried in nest of thick adhesions. Many enlarged glands. Cholecystectomy. Note resemblance to findings in other syphilitic gall-bladder cases.

Chart B. Well for two years, then complains of pain in upper abdomen and thinks mass is reappearing. No mass found, liver not felt, but sense of resistance interpreted as highly developed rectus muscle. This was in 1917.

N Blood Wassermann Test.

Chart C. 1919. Pain in Right Shoulder, sudden, sharp. Also in old laparotomy scar. Severe, almost suffocating attacks of pain under right costal margin. Lost weight and strength. (Recall patient had had gall-bladder removed.)

Mass Felt in Left Epigastrium. Moves with respiration, enlarged liver felt.

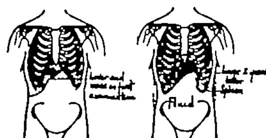
Blood Wassermann Taken for First Time, Positive.

Exploration Advised by Diagnostician, Refused by Surgeon.

Prompt and Complete Recovery Under Treatment for Syphilis.

Fig. 887

THE "LATENT LIVER" AND THE OVERLOOKED WASSERMANN TEST



Woman, aged twenty-eight.

Examined 1919. Complained of nausea, weakness, and sore stomach. Intermittent attacks of pain in right hypochondriac region, with pain in right shoulder. Palpable mass moving on respiration was felt in right epigastrium, and later identified as liver. The test meal and stomach and chest x-rays were negative.

Preliminary Diagnosis. "Old pyloric ulcer with inflammatory tumor 50 per cent.; pylorospasm, 50 per cent., neurosis.

The Patient Admitted She Felt Better When Among Friends or Friendly People.

Final Diagnosis. "Palpable epigastric mass—liver. Treat for bowels. Neurosis.

N Blood Wassermann Test Taken.

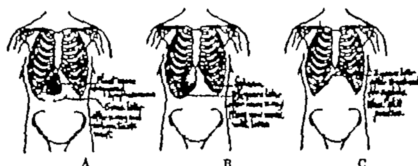
Two Years Later the Patient Returned. She had had all her teeth pulled, without result. The liver was larger than before, the spleen palpable, and there was now free fluid in the abdomen. She had vomited blood once and had had fever to 103 degrees at times. All her symptoms were now referable to the hepatic cirrhosis.

Blood Wassermann Test: Strong positive. History of primary syphilis at age nineteen, overlooked in first examination, now obtained.

Look for Syphilis Early in the Examination When the Liver is Palpable.

Fig. 668.

GUMMA OF THE LIVER, FIXED IN THE EPIGASTRIUM BY ADHESIONS, MAY BE MISTAKEN FOR A RETROPERITONEAL NEOPLASM



Male, aged eighteen, first examined in 1917

Nodular Mass Right Upper Abdomen: Very tender does not move with inspiration. Probable retroperitoneal lymphosarcoma. x-Ray chest negative.

N Blood Wassermann Test Taken. x-Ray Treatment Begun.

Five Months Later: Mass thought to be larger (In reality this was probably the liver edge) **Further x-Ray and Radium Treatment.**

Three Years Later: Mass as indicated at B. General health unchanged. Spleen recognized.

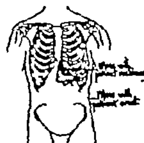
First Wassermann Test Taken Strongly and repeatedly positive.

Diagnosis Revised: Mass now moves with respiration. Liver identified. "Syphilitic hepatitis with gumma.

Two Years Later After Treatment for Syphilis: Liver almost normal, spleen no longer palpable, general health excellent, blood Wassermann positive.

Youth, N History of Infection, Fixation of Mass and Lack of Wassermann Led to This Diagnostic Error Source of Infection Unknown.

Fig. 669.



A GUMMA OF THE LEFT LOBE OF THE LIVER MAY BY DISPLACEMENT SIMULATE A PANCREATIC OR MESENTERIC TUMOR

Woman, aged thirty-seven.

This Patient's Syphilis was Recognized before operation, but exploration wa concerred in by all consultants because of the bizarre physical findings.

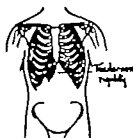
A Lobulated Mass, Almost Suggesting Bunch of Grapes, could be felt and pushed about in the left upper quadrant. It did not seem to respond especially to respiratory movement.

At Operation, Saucer-like Gummatous Plaque 8 10 cm. in size, ith pie-segment divisions, was found in the left lobe of the liver The pancreas and mesentery ere normal.

The Mass Disappeared Under Treatment for Syphilis.

Almost Any Physical Finding May be Compatible with Syphilis in the Upper Abdomen. There is No More Untrustworthy Criterion.

Fig. 670.



SIMULATION OF GALL-BLADDER MALIGNANCY AND CARCINOMA OF THE LIVER BY SYPHILIS. NO PREOPERATIVE WASSERMANN TEST TAKEN

Man, aged forty-two.

Examiner's Summary "Tenderness marked in region of gall-bladder with slight rigidity Gastric -ray—three trials with belladonna—reports mass, extrinsic, stomach and duodenum negative.

Preliminary Diagnosis: Subacute cholecystitis.

Final Diagnosis: Probable malignancy of the gall passages, though possibly infected gall-bladder in anomalous position. Explore.

No Blood Wassermann Test Taken.

Operative Findings: "Liver filled with metastatic tumors, all sizes, having appearance of being malignant. Piece removed from one was found to be necrotic and did not show carcinoma, but clinically it is carcinoma. Gall-bladder contained no stones. Origin of carcinoma undetermined.

Pathologic Report: Necrotic Fibrous Inflammatory Tissue.

x-Ray Therapy was Ordered.

Comment on History two years later after 12 x-ray treatments with little change: "Inclined to question diagnosis.

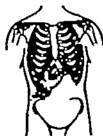
First Blood Wassermann taken one month after above comment Strong positive.

Palpable Mass and Enlargement of Liver with All Symptoms then Disappear under treatment for syphilis (6 arsphenamin injections).

Operative Appearances May Deceive. Take Wassermann Before Exploring.

Fig. 671.

CARCINOMA OF THE LIVER IN SYPHILIS



Man, aged forty-nine.

This Patient, Apparently in Excellent Health and weighing over 200 pounds, complained of upper abdominal distress.

Physical Examination: Large hard rounded nodular liver containing definite masses on anterior surface. Pupils fixed to light. No jaundice or ascites.

Stomach Examination: Achlorhydria, 400 c. retention. Ray reported *negative*.

Blood Wassermann Reaction Positive.

Neurologic Examination: Tabetic neurosyphilis with positive spinal fluid.

Diagnosis Hepatic cirrhosis (?). Possibly non-specific hypertrophic cirrhosis.

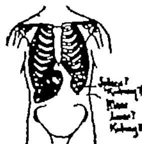
Treatment: Two injections of arsphenamin intravenously 0.3, 0.4 gm.

Result Rapid development of ascites and edema of the legs. Death. Cause of death, clinical, nephrosis (?)

Autopsy: Massive *carcinomatosis of liver* from primary adenocarcinoma in pyloric ring. Pancreas, kidney etc., negative.

Comment: Had it not been for the confirmatory neurosyphilis we might have thought this an example of false positive blood Wassermann in carcinoma. Apparently arsphenamin can cause Herxheimer reaction in carcinomatous liver, for no other explanation of the ascites and fatal outcome seems vailable The excellent condition of the patient and the report of negative -ray of the stomach led to premature dismissal of the diagnosis of carcinoma, although the retention should have suggested it. The achlorhydria occurs in both syphilis and carcinoma.

Fig. 672.



THE SYPHILITIC LIVER AND SPLEEN MAY BE CONFUSED WITH DISPLACED OR PATHOLOGIC KIDNEYS

Woman, aged twenty-nine.

Medical Diagnosis before entering clinic "prolapsed kidney." Given a special corset, no relief. No Wassermann test taken. Had had attacks of right subcostal pain with fever.

Preliminary Diagnosis: Both masses appear to be kidney or extend back to kidney region.

Urologic Examination: Indeterminate renal condition, right kidney function twice that of left. Possible polycystic kidney bilateral, with slight infection right.

Blood Wassermann Reaction: Strongly and repeatedly positive.

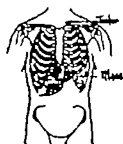
Final Diagnosis: Mass right upper quadrant has physical characteristics of hepatic tumor. With effect of salvarsan.

Three Months Later: Hepatic mass reduced 80 per cent., spleen 20 per cent.

Good Recovery: Observation four years.

The Blood Wassermann and the Spinal Fluid Examination are Remarkable Clarifiers of Puzzling Abdominal Pictures.

Fig. 673.



DIAGNOSIS OF "PANCREATIC CYST" MADE WITHOUT PREOPERATIVE WASSERMANN TEST. GUMMA OF RIGHT LOBE OF LIVER FOUND AT OPERATION

Woman, aged fifty-three

Chief Complaint. Cancer of stomach and other tumors (*x-ray* diagnosis before entry)

1910 Operation for Gall-stones (cholecystectomy)

1911 Appendectomy

1921 *Large Nodular Hard Mass*, whole upper abdomen. Moves with inspiration.

Preliminary Diagnosis. Metastatic carcinoma (?).

Final Diagnosis: *Large pancreatic cyst.*

Operative Diagnosis. Multiple tumors of the liver, largest 8 x 8 cm. in diameter involving entire left and palpable parts of right lobe of liver. Dense adhesions from previous operations. Much perihepatitis. Gall-bladder seen but not accurately examined because of adhesions. Stomach negative, pancreas negative. One tumor 5 cm. in diameter attached by narrow pedicle removed for diagnosis. Investigate patient for syphilis.

Pathologic Report. Chronic hepatitis.

Postoperative Blood Wassermann Test. Strongly positive.

Recovery Under Treatment for Syphilis.

A Routine Wassermann Test is Surgical Forethought.

Fig. 674.

SPLENOMEGALY AS A CAUSE OF GASTRO-INTESTINAL HEMORRHAGE. X-RAY DIAGNOSIS OF DUODENAL ULCER. SPLENIC ADHESIONS TO STOMACH. NO ULCER FOUND. MASSIVE GUMMATOUS HEPATITIS

Female, aged forty-two, housewife.

Chief Complaint Six severe gastric hemorrhages in three years. Onset five years ago. Gas and bloating of lower abdomen.

Distress Relieved by Appendectomy

Hemorrhages Prostrating, twice required transfusion. None for past year

x Ray Diagnosis One Year Ago Ulcer near pylorus.

Physical Examination No thoracic or abdominal signs. Twenty-five pounds over weight. Hgb., 60 per cent. Test meal: Free HCl 16, total 30

x Ray of Stomach (three successive examinations with belladona).

Final diagnosis, Duodenal Ulcer

Blood Wassermann Reaction Repeated strong positive.

Preoperative Antisyphilitic Treatment: No distinctive response.

Clinical Diagnosis Bleeding duodenal ulcer

Operation No Ulcers Found. Stomach Very Large Duodenum Enlarged and Thickened. Large Gummatous Mass in Liver Spleen Five Times Normal Size Adherent to and Pressing Upon Stomach in the Middle.

Splenectomy Performed.

Pathologic Report Diffuse chronic splenitis.

Excellent Recovery

Discussion

1. The hemorrhages were interpreted by Dr W J Mayo as caused by the splenomegaly and may have been due to esophageal varices.

2. Some of the roentgenologic appearances suggesting duodenal or gastric ulcer were possibly due to the effect of the adhesions between spleen and stomach.

Fig. 675

EFFECT OF SPLENECTOMY ON A CHRONIC ANEMIA ASSOCIATED WITH SYPHILITIC HEPATITIS AND CHRONIC SPLENITIS

Woman, aged forty-three, married.

Chief Complaint Abdominal tumor

First symptom, fulness in epigastrium, three years ago.

Attacks of pain in right hypochondrium.

Gradually increasing sallowness, two years

Possible syphilis by previous marriage, but no definite history No miscarriages.

Examination

Marked pallor moderate emaciation.

Large liver roughened and firm.

Spleen, 8 cm. below costal margin.

Ascites moderate.

Blood findings Hemoglobin 40 per cent.

R.B.C. 2,800,000,

W.B.C. 8600

Differential negative.

Blood Wassermann reaction Strong positive.

Treatment Mercurial inunctions and iodid.

Re-examination Two years later Moderate improvement.

Hgb. 48 per cent. after 6 injections neosalvarsan.

Hgb. 64 per cent., fell to 55 per cent. after second course of arsphenamin.

Chronic slight icteric tinge, no increase in hemoglobin above 55 per cent.

Feels well.

Blood Wassermann negative.

Splenectomy 5/29/19 Spleen three times normal size, hobnailed cirrhotic liver.

Many firm adhesions.

Marked fibrosis and destruction of malpighian bodies.

Hemoglobin 66 per cent. eleven days after operation.

No Further Treatment for Syphilis.

Hemoglobin 68 per cent. one year later

R.B.C. 4,470,000,

W.B.C. 4600

Differential count normal.

Hemoglobin Three Years and Four Years Later 65 to 70 per cent.

Blood Wassermann Reaction fluctuating between positive and negative since.

Definite Improvement in General Health.

Hysterectomy and salpingectomy for salpingitis and fibroids, 5/12/20

Still Has Chronic Pallor but Good General Health.

Fig. 670.

SYPHILITIC HEPATITIS AND SPLENITIS WITH VIOLENT HERXHEIMER REACTION FOLLOWING ARSPHENAMIN RECOVERY UNDER MERCURY AND IODIDS FOLLOWED BY RECURRENCE OF JAUNDICE AND DEATH FROM ACUTE YELLOW ATROPHY. ICTERUS GRAVIS (?). HEPATORECURRENCE (?). INFECTIOUS JAUNDICE WITH ACUTE YELLOW ATROPHY (?).

A man, aged thirty-two years, laborer

Examined 1/12/1923

Chief Complaint: Jaundice of two weeks duration.

Had consulted a physician because of pallor and malaise.

Was told he had large spleen and "hemolytic jaundice

Splenectomy advised.

Apparently as preparation, was given 3 injections of neo-arsphenamin, on three successive days (Pollitzer system)

Violent Turn for the Worse. Jaundice deepened, abdomen now large and tense

History of Previous Jaundice for three days, one year before.

Pain in right hypochondrium for one month

\ attacks

Examination: Deep jaundice.

Liver down to umbilicus, hard. Spleen the same. Jaundice deep. No fluid w va, no edema of the feet. Blood-pressure 185/90.

Urine negative except for bile, urobilin, and urobilinogen.

Blood urea 16 mg per 100 c.c.

Blood Wassermann Reaction Strongly positive

Treatment Rest in bed.

Sodium iodid intravenously Mercury succinimid intramuscularly

Violent Mercurial Colic

Changed to mercury with chalk and potassium iodid

Improving Succinimid and sodium iodid resumed better tolerated

After One Month Mercurial and Iodid Preparation, given 3 arsphenamin injections without incident

One Month Later All Jaundice Disappeared.

Felt ell, weight best in years.

Resumed Mercury and Iodid for two Months because of recurrence of epigastric pain.

Treatment Discontinued One Month. Felt well.

Without Warning Jaundice Began to Return. Stools clay colored. Some diarrhea following constipation.

Returned to Clinic Six Weeks After Reappearance of Jaundice.

Liver as large as before, spleen not so large. Jaundice very deep.

Ray showed aortic calcification.

Albumin in urine moderate in amount, bile urobilin, and urobilinogen.

Free fluid present in abdomen.

Blood Wassermann Reaction Still Positive.

Treatment: Fluid reduced by free catharsis.

Mercury succinimid ½ grain daily

Iodid by mouth. (hence intravenously

Restriction of fluids.

Kidneys began to react and ascites increased.

Mercury colic reappeared. Patient howled with pain.

Paracentesis. Mercury stopped.

Patient Lost Ground Steadily: Mercury resumed in smaller doses.

Sulpharsphenamin 0.1 gm. intramuscularly

Blood Urea Going Up: Colic better

Blood urea 72 mg per 100

Emaciated and very toxic Extreme jaundice. Hemorrhage from bowel

Iodid stopped.

Blood Urea Four Days Before Death, 1?? mg.; t days before death, 184 mg.

Creatinin (blood) 3.8.

Death in Coma.

Necropsy Findings Destructive hepatitis (liver eighed 978 gm —syphilitic) intense jaundice, syphilitic splenitis (340 gm), acute diffuse nephritis, local hemorrhagic pancreatitis.

DISCUSSION

On this patient retura with his second ttack of jaundice I nalyzed his situation as follows

1 Probably combines two pictures ith the following order of events:

( ) Syphilitic hepatitis and splenitis with tremendous Herxheimer flare-up following the 3 neo-arsphenamin injections before entering the clinic

(*b*) Recovery from the Herxheimer and improvement in liver and spleen under continued mercurial and iodid treatment.

( ) Mercury colic and intolerance of iodids interfere ith treatment before and now Make intensive treatment almost impossible

(*d*) Tw months comparative good health show effect of previous treatment.

(*e*) Now has recurrent syphilitic hepatitis, hepatorecurrence (Milian), or

(*f*) Superposed infectious hepatitis hich in combination with the previous cirrhosis has produced the present extreme jaundice and ascites —

Fig. 676 (*Continued*)

2. As his case progressed, the signs of acute yellow atrophy destructive hepatitis, became apparent in the shrinkage of the liver the abdominal distress, and the deepening jaundice and emaciation. No leucin or tyrosin was recognized in the urine. The patient proved unable to carry even moderately intensive treatment, so that it was impossible to combat the condition as a syphilitic acute yellow atrophy. The nephritis and mercurial colic prevented mercurialization, bloody diarrhea followed iodids, and we hesitated at large doses of arsphenamin lest the arsenic simply hasten the process. Milian contends that arsphenamin is indicated.

3. Acute yellow atrophy may be part of the picture of late arsphenamin poisoning, a syphilitic relapse following inadequate treatment, or a complication of epidemic infectious jaundice. In this case it was impossible to identify the etiology impossible to treat the condition, and the fatal outcome was inevitable.

4. We have secured a good result in a similar case by the foregoing measures.

5. Note that the first flare-up, in which the liver was undoubtedly damaged seriously followed intensive use *of arsphenamin without mixed preparation*. The Pollitzer type of system may have disastrous results if misapplied in this way.

6. Bismuth as now used might have saved the situation for this patient.

Fig. 677

THERAPEUTIC PARADOX AND RELAPSE IN HEPATIC SYPHILIS

Case A, Male, aged forty-seven. 1921.

Syphilitic Hepatitis and Splenitis. Liver 6 cm. below costal margin. Spleen 3 cm.

Treatment. One week Hg. succinimide, 6 injections arsphenamin 0.2 to 0.3 gm.

Result: Liver and spleen subside much improvement. Home on inunctions.

Returns. Good condition, no fluid, but duodenal ulcer produces symptoms.

Diagnosis of Hepatitis Confirmed in operation for duodenal ulcer. Evidently active.

Neglects Treatment ten months. Marked ascites develops.

Hospital Care, Purgation, Iodid, slightly improved. Sent home on mercury with chalk.

Urine Contains Much Pus.

Returns After Five Months Much Improved on mixed treatment. Continued.

Returns After One Year. Sudden increase in fluid three months ago. Tap elsewhere followed by bloody and watery diarrhea.

Patient in Extremis. Sent home. Puncture of bowel (?).

Case B, Male, aged thirty-eight. 1919

Syphilitic Hepatitis. Recognized two years ago. Pain and jaundice.

Treatment. Mercurial injections and iodid. Inunctions.

Ascites Appeared one week ago.

First Arsphenamin Injection one week ago, elsewhere. Large dose (?).

Markedly Worse after Injection. Abdomen greatly distended with fluid. Immediate tapping required.

Treatment. Inunctions and iodid, the latter by mouth and rectum.

Grew Rapidly Worse. Fluid Overload, **No Catharsis, Repeated Tappings,** four times in thirty days, 7 to 12 liters each.

Patient Failed Rapidly. Anasarca.

Died. Two months later.

Discussion

1. **Both These Cases Might Seem to Suggest the Ill Effects of Arsphenamin** on hepatic syphilis. Case A, however had only good results even from arsphenamin at the outset until he had neglected treatment ten months, when ascites began to develop. The operation had shown an active hepatitis, not healing, so that the ascites could hardly have been due to shrinkage and scarring.

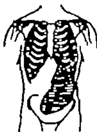
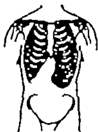
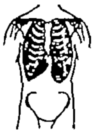
2. **Case B Illustrates the Immediate Unfavorable Effect of an Unknown but probably large dose of arsphenamin.**

3. **Note the Contrast in the Course of the 2 Cases from the standpoint of the management of their ascites.** A was controllable by catharsis and fluid restriction. B by fluid overload, no catharsis and repeated tapping, was thrown into a vicious cycle.

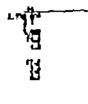
4. **Case A Might Have Been Saved by Persistence in Arsphenamin, Mercury and Iodid treatment.**

5. **Case B Might Have Been Saved by Our Present Knowledge of the Management** of ascites in syphilitic hepatitis.

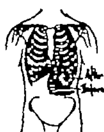
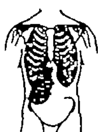
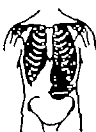
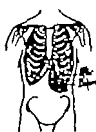
6. **Note the Pus in the Urine of Case A.** Perhaps a failing kidney contributed to his relapse of ascites. Such points should be watched.





D

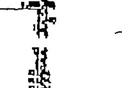




Fig. 678.—A group of cases illustrating various aspects of the hepato-splenic complex from the standpoint of blood picture, clinical diagnosis, and therapeutic response. Note syphilitic Banti complex.

CHAPTER XIX

SYPHILIS OF THE CARDIOVASCULAR SYSTEM

General Considerations.—The successful diagnosis and treatment of all special aspects of late syphilis lie in the detection and effective treatment of early syphilis in general. In no field has this apparent truism greater need of appreciation than in that of cardiovascular syphilis. Brunsgaard's clear-cut demonstration that cardiovascular disease, even more than neurosyphilis, is the Nemesis of the infection and the outcome of more than a third of fatal syphilis, cannot be too constantly borne in mind or too frequently impressed upon the medical student and upon the practitioner. Even our earliest clinical recognition of vascular involvement in this disease is unhappily comparatively late. The reason is obvious: there exists no rubric for its early detection, no sign manual like the abnormal spinal fluid to serve as a warning. Even the blood serological tests fail more often in the detection of this particular aspect of the disease. The teaching in this field, both by internists and syphilologists, has been anything but preventive. Generations of bowing at the shrine of the spectacular in physical diagnosis have led inevitably only to the identification of consequences. The demonstrator's voice rings out in triumph: the medical students crowd around the *cor bovinum* and the hat-box aneurysm: they observe with enthusiasm the thrill, the buzzing and whirring, the heave, the sound of the pistol shot. Seldom indeed does one find an equal degree of absorption or an equal frequency of demonstration of the still, small signs and symptoms of the preventable onsets of syphilitic cardiovascular disease. Until teacher and textbook turn from the parading of consequences in the amphitheatre to devote themselves to anticipatory watching in the office and consultation room, to habitual suspiciousness in observation, and to an acute analysis and ferretting out of veiled beginnings, syphilis of the heart and aorta will remain the great burying ground of the disease and the clinician's perpetual Waterloo at the hands of the postmortem pathologist.

The high points of syphilis of the cardiovascular system may be touched in three words: ubiquitous, insidious, disastrous. Vascular distribution of the infecting agent and injury to the blood vessels form the groundwork of the pathology of syphilis. It follows, then, that in almost any clinical aspect of the disease and in any method of classifying its morbid phenomena, a vascular element will be apparent. Vascular change underlies the necrosis of gumma, the absence of hemorrhage from the syphilitic gastric ulcer, the smooth, serum-discharging surface of the chancre with its hemorrhagic border. It may underlie the hemiplegia that follows rupture or thrombosis of the lenticulostriate artery in the internal capsule, or the anginal syndrome that follows syphilitic sclerosis of the coronary vessels. It is apparent, then, that no small part of syphilis of the vascular system will appear in the consulting room under the clinical mask of disease of other structures and may even fail to present any distinctive symptomatic earmarks whatever. This is particularly well illustrated by the longstanding controversy over rheumatic aortic valve disease and the differences of opinion as to a specific symptomatology for uncom

plicated syphilitic aortitis which has run the gamut from itemized tables of signs to the blanket assertion that uncomplicated syphilitic aortitis cannot be *diagnosed in life until complications appear Certain groups of vascular* phenomena may be recognizable as in syphilis of the nervous system, by certain symptoms and signs, but it may nearly always be assumed that when one tenth of the process is causing symptoms which come to clinical recognition, nine tenths with its antecedents and consequences, lie below the threshold of clinical recognition. It is this submerged nine tenths of disease of the vascular system which so frequently brings the clinician to chagrin at the hands of the pathologist, who discovers postmortem the real extent of the vascular change which syphilis produced with this minimum of symptomatic expression. Following the often mistaken or irrelevant lead of the chief complaint, the clinician is too often led astray by the prospective victim of syphilis of the cardiovascular system who, if he consults the physician at all in the early years of his disease, seeks treatment for some obvious or painful lesion such as gummatous osteomyelitis, late cutaneous recurrence, iritis, or tabetic neurosyphilis Even with every consideration for the difficulties that must confront the diagnostician in dealing with cardiovascular syphilis, there is no escaping the disconcerting demonstration recently brought forward by Moore, Danglade and Reisinger that the "index of suspicion even of a highly trained medical group toward syphilitic aortic disease is much lower than the circumstances warrant. Moore (1943) points with justifiable pride in a recent revision of his text to the fact that overemphasis, if it can be called such on a categorical list of symptoms and signs, some of which have even been proved not to be specific, has raised the percentage of the preautopsy diagnosis of uncomplicated syphilitic aortitis in the Johns Hopkins Hospital from 0.2 per cent to 26.3 per cent. Thus, indeed, is almost the crux of the matter Hypersuspicion has its place and will raise the index of suspicion of a medical group to the point where a search for collateral evidence and therapeutic tests will confirm many diagnoses and save a number of lives.

I 105 necropsy cases of uncomplicated syphilitic aortitis, the clinical diagnosis as correctly made in only 4 during life and in 13 more it was suspected that something was wrong with the aorta. On the basis of the symptoms and physical signs recorded the diagnosis might have been correctly made in 35 additional patients. Thirty-four patients died with hearts and aortas thought clinically to be normal.

It may be said with emphasis, then, that only by the most habitual and painstaking examination of the patient as a whole are the early signs of cardiovascular degeneration to be detected Not only must the signs be recognized, but they must be correctly interpreted The more one looks for cardiovascular syphilis in clinical material of whatever type the more one finds. The better one knows the earlier and the concomitant signs of syphilis as a disease the more cardiovascular syphilis he may detect at a time when its detection means some hope of recovery and not merely a veiled death sentence. It is, in fact, the examination of the well patient rather than the ill one which is the preventive crux in cardiovascular syphilis, as in all disease.

Historical Considerations and Literature.—Lancisi is credited with associating aneurysm with syphilis clinically in 1728. Wagner while still confusing the disease with atheroma, made an accurate macroscopical study and Döhle description connected the pathologic picture with syphilis in young man suffering undoubtedly from the infection. For a time the disease was known as the Döhle-Hellerschen form of aortitis. Welch, the British observer is credited by

Allbutt with the full establishment of clinical knowledge of the disease by his publication in 1873 of study of 117 cases of "fibroid aortitis, in 46 per cent of which syphilis was definitely present. The finding of *Spirochaeta pallida* in the aortic wall was first accomplished by Reuter in 1906, by Benda in the same year by Schmorl in 1907 and by Wright and Richardson in this country in 1909 The aortitis of congenital syphilis, discussed elsewhere, has been recognized since the observations of Wiesner in 1905, and the abundance of the organisms in the involved tissues in spite of the relative paucity of clinical findings has been confirmed by Rach and Wiesner and Warthin. Typical lesions have been described by Klotz.

Both on the clinical and the pathologic side, American contributions have been numerous and distinguished. During the past two decades in particular they have contributed greatly to the clarification of the entire field. Though, as he modestly asserted, Virchow foreshadowed from gross pathologic lesions some of the most striking aspects of syphilitic cardiovascular disease, it has been Warthin s technical mastery of the problem and his unrivalled persistence and patience as an investigator which have brought conviction of the ubiquity of vascular syphilis home to the medical profession at large. His insistence that microscopical findings, rather than gross path ologic changes in aorta and myocardium, are the crucial point in postmortem diagnosis, has been chief factor in broadening our conceptions of this aspect of the disease. Though they have inevitably aroused controversy and have accentuated lines of cleavage between the gross pathologic and the microscopical pathologic schools, as well illustrated, for example, in the writings of Symmers and Martland, Warthin communications have the justifiable finality of statement which only the presence of *Spirochaeta pallida* with waxed moustaches" in his microphotographs and sections can give. Klotz has clearly defined the lymphatic and periaortitic factors in the pathology of syphilitic aortitis. Reid has done much to connect pathologic findings, pathologic physiology and clinical observation in the field.

On the clinical side the American student should read particularly Allbutt' monograph, the volume by Hirschfelder the important publications of Osler Brooks, Longcope, Elliott, Pardee, Reid, Hoover Willius, Stroud, Henrichsen, Kampmeier Blackford and Smith. Most recent and extremely important are the symposium on cardiovascular syphilis before the American Heart Association in 1930, the report of the CCG (1930), the papers of Wile on therapeutic paradox, and the direct examination of treatment results by Carter and Baker and by Moore, Danglade and Reisinger containing, in addition to their own results, critical summaries of the entire diag nostic and therapeutic fields. The Continental and especially the German contributions are massively presented in the sections by Herxheimer Evelbauer and by Schlesinger in the Jadassohn Handbuch. The observations of Langer on the incidence of aortitis, and of Hubert, Frandel, Horder Kotlsey-Möller-Doham, Schottmüller and Schlesinger, have had great influence in the development of current treatment conceptions.

Among the authors contributing evidence for and against the possibility of diagnosis of uncomplicated syphilitic aortitis are: Kampmeier Glass and Fleming (1942)· Nichols (1940); Hearn (1946); Dressler and Silverman (1945) Bekaras, Hollander Goldsmith (1941); Maynard (1948); White and Wise (1937); Howles (1943); Maynard, Curran, Rosen, Williamson and Lingg (1935)

The Frequency of Syphilitic Cardiovascular Disease.—The current estimates of the incidence of cardiovascular syphilis vary with the age group, the race, the sex, and the degree of emphasis placed on microscopical as compared with macroscopical criteria. Aortic syphilis at autopsy is, of course, enormously more frequent than clinically recognized syphilis of the cardiovascular mechanism Cardiovascular syphilis constitutes from 10 to 15 per cent of all cardiovascular disease, according to the estimates of the Metropolitan Life Insurance Company (cases over fifty), Wykoff Lingg (1001 cases) and Carter and Baker (5323 Johns Hopkins cases of cardiac disease) From these various figures Moore, Danglade and Reisinger estimate that about 240 000 persons in the United States at any one time have cardiovascular syphilis, and 20 000 of these die each year

In study of 6000 patients with untreated late syphilis Turner reported that approximately 10 per cent showed definite clinical evidence of cardiovascular damage. Clawson and Bell, in 4877 necropsies, found that 126 cases (2.6 per cent) were syphilitic aortitis. Martland, from Newark City Hospital and Essex County New Jersey coroner material, found among 6067

cases investigated 1590 cases of sudden death or 18 per cent were due to heart disease. Three hundred or 18 per cent were autopsied, of these 60 were rheumatic hearts, 101 were syphilis of heart and aorta and 139 were arteriosclerotic heart disease. In 6233 patients with late or latent syphilis studied by the CCG (1936) 619 patients, or 9.9 per cent, had evidence of syphilitic cardiovascular disease, of which 4.9 per cent had uncomplicated syphilitic aortitis, 4.1 per cent syphilitic aortic regurgitation, 1.2 per cent syphilitic aortitis with saccular aneurysm, and 0.3 per cent syphilitic myocarditis. Gelperin (1940) in a study of autopsies performed at the Cincinnati General Hospital from 1926–1937 found an average incidence of 9.1 per cent of syphilitic aortitis. McDermott, Tompsett, and Webster (1942) found an incidence of 3.4 per cent of aortic regurgitation among 2718 syphilitic patients.

Langer in the enormous material of the Rudolph Virchow Krankenhaus in Berlin (43,106 autopsies), found 70 to 80 per cent of the syphilitic patients to have cardiovascular involvement. Warthin in the decade from 1909 to 1919 found cardiovascular syphilis, using both gross and microscopical criteria, in 97.6 per cent of syphilitic patients; and in the decade from 1919 to 1929, in 86.3 per cent.

The contrast of pathologic with clinical diagnostic figures is illuminating. Of Langer's material, 39.3 per cent of cases of syphilitic cardiovascular disease were diagnosed in life. Lucke and Rea found 43 per cent clinically diagnosed in life. Moore, Danglade and Reisinger found 16.2 per cent diagnosed in life.

Cardiovascular syphilis is from two to four times as common in males as in females, the higher proportion applying especially to white patients, as in Stokes's experience with Mayo Clinic material.

In 6420 cases in Baltimore, Turner found 13.9 per cent of males and 6.7 per cent of females to have cardiovascular disease; one and one-half to two times as many Negroes as whites have cardiovascular disease. Paullin, in 600 cases of heart disease in Negroes, found 38.8 per cent to be syphilitic. Of 619 patients with cardiovascular syphilis reported by the CCG (1936) 441 were males, 178 females. Of the 6233 patients with late or latent syphilis studied, 8.1 per cent of the white males, 31.0 per cent of the colored males, 6.1 per cent of the white females and 12.8 per cent of the colored females presented evidence of cardiovascular syphilis. In a study of 633 cases of syphilitic aortic aneurysm, Kampmeier (1938) reported an incidence of 3.7 males to 1 female among the colored, and 7.9 males to 1 female in white patients. Of the 633 cases 76 per cent were Negroes, 24 per cent white.

The question as to whether cardiovascular syphilis is on the increase or not is, of course, an important one both for diagnosis and treatment. Langer believes that the steady rise in the proportion of cardiovascular syphilis among syphilitics from approximately 35 per cent in 1907 to approximately 65 per cent in 1922 to 1925 is the product of modern treatment methods, particularly the use of the arsphenamines. On the other hand, Moore, Danglade and Robinson, examining Langer's figures, reached the conclusion that the apparent increase is the result of added pathologic experience, particularly in microscopical diagnosis. In a study of 3641 cases of syphilis treated during the early stages of the disease, the CCG (1930) reported only 26 cases (less than 1 per cent) which subsequently developed cardiovascular syphilis. Of 103 cases followed for ten to twenty years, 6.7 per cent developed cardiovascular disease but in none did syphilitic aortic regurgitation or aneurysm develop.

The Age of Onset.—Cardiovascular syphilis is recognized in middle life, by far the larger number of patients coming to diagnosis between the ages of thirty five and fifty five.

In 406 cases of syphilitic aortic disease at the Buffalo City Hospital Levitt and Levy (1940) found 78.9 per cent were between thirty-one and sixty years of age. Nichols (1946) reported the average age of patients in whom aortic insufficiency was diagnosed to be 48.0 years, with 73.6 per cent diagnosed between the ages of forty-one and sixty years. In 843 Negroes with syphilitic

aortic insufficiency Blackford and Smith (1938) found an average age of thirty-seven years. Of 926 patients with uncomplicated syphilitic aortitis, the CCG (1936) reported 9 per cent developed before the age of thirty years, the highest incidence (39 per cent) diagnosed in the thirty-five–forty-five age group.

The role of cardiovascular syphilis as Nemesis, its trick of taking toll of the years of mature achievement, the best of middle life, is very apparent and indicates at the same moment its enormous costliness to the community and the danger of social criteria in its diagnosis. Many young man without footbold in the world when he acquires his primary lesion at twenty is member of the substantial business or professional community when his vascular degeneration overtakes him. He is then, to his own detriment perhaps, too respectable in the eyes of his medical advisor or his life insurance examiner to have syphilis seriously considered, or he has forgotten its obscure beginnings (Fig. 679).

Duration of Infection at the Time Patients Seek Advice.—Very little cardiovascular involvement is recognized in the first decade of the disease. Forty five per cent is recognized in the second decade, 30 per cent in the third. Improvement in the present state of diagnosis must, then, be made by setting our clocks ahead a decade or two, so to speak, and studying the patient in his first five to ten years after infection, if we hope to anticipate irremediable damage.

Maynard, Curran, Rosen, Williamson, and Lingg (1933) reported that in 100 patients with syphilitic cardiovascular disease in which the duration of the infection was known, 25 per cent showed evidence of cardiovascular syphilis within ten years after the occurrence of chancre, although the mean interval was twenty years. In 170 cases of cardiovascular syphilis reported by Wile and Snow (1936), the duration of the disease was over fifteen years in 90 per cent of the cases. Of 196 patients with uncomplicated syphilitic aortitis in which the duration of the disease was known, the CCG (1936) noted 10 per cent were diagnosed less than five years after onset of the disease, 3 cases diagnosed in the second year of infection. Kampmeier (1938) reporting on 243 patients with aneurysm found the peak at sixteen to twenty years, approximately half of the patients being in the eleven to twenty year post-infection group.

There are, of course, number of well-authenticated instances of precocious involvement of the cardiovascular system with early clearly recognizable clinical signs. Among these should be, of course, included the hemiplegic accident of neurorecurrence. Reid records case in which young man infected in June had definite evidence of aortic involvement by August and enough signs for positive diagnosis in September three months after infection. Harlow Brooks observed case in which death resulted from perforation of the aorta just above the valves before the secondary eruption was fully developed. Osler noted an aneurysm of cerebral artery eighteen months after the chancre. Osler also describes in the Schorstein lecture (1909) the case of "a young man aged nineteen in the early secondary stages of syphilis who as shoving up side of beef but it came back on him so that he had to let it down. He tried again and again and at last succeeded. He was faint and tired, and soon felt severe pain in the abdomen. Shortly afterward he developed large aneurysm of the abdominal aorta. Blackford and Smith (1938) reported that eight months after dark-field examination had revealed the treponema, boy of eighteen years of age who had received no antisyphilitic treatment experienced sudden, excruciating chest pain. Cardiac failure followed promptly with signs of aortic insufficiency when examined by us. H died three weeks after onset. Autopsy revealed rupture of gummatous aortic cusp. Additional case material is reviewed on page 904. From the pathologic physiology of syphilis it is difficult to understand how the heart and great vessels can ever escape involvement, and the remarkable clinical fact is not that they are involved, but that the involvemen is comparatively benign in the early stages.

Effect of Occupation.—In a study of occupation of 1000 syphilitic patients, Cochems and Kemp (1937) conclude that physical exertion seems to contribute toward the graver forms of syphilitic cardiovascular disease. Osler said that Venus, Mars, and Vulcan were the triad responsible for aneurysm In 633 cases of aneurysm reported by Kampmeier (1938) approximately 60 per cent were laborers. In 210 cases of cardiovascular syphilis studied by Wile

Fig. 879.

CARDIOVASCULAR SYPHILIS (ANEURYSM) UNDER TREATMENT. SYMPTOMATIC IMPROVEMENT. REDUCTION IN SIZE OF ANEURYSM. PROGRESSION OF ELECTROCARDIOGRAPHIC SIGNS OF MYOCARDIAL DEGENERATION IN SPITE OF TREATMENT

Salesman, aged fifty-three years, married.

Examined 7/6/1920.

Chief Complaint: Hoarseness and suspected aneurysm (home physician). Below par for three years. Woke up hoarse six weeks before coming to Clinic.

Lit Insurance Examination Seven Years Before. Aortic Murmur Recognized, but Apparently Ignored. Went on about his business and played golf.

General Health Good, though thin and of poor color for years.

Denies Venereal Infection. On Close Questioning Recalls Penile Abrasion Thirty-five Years Ago.

Blood Wassermann Reaction. Negative at home. **Strong Positive now.**

Has Been Taking Mercury and Iodid.

First Examination

Heart much enlarged. Double murmur all over chest, loudest at first and second interspaces.

No thrill.

Dulness over manubrium 8 cm. wide.

Slight diastolic shock.

Tracheal tug.

Blood-pressure 210/70.

Paralysis of right vocal cord.

x Ray, Small Aneurysm of Arch. Heart enlarged.

Diagnosis. Aortic aneurysm with aortic regurgitation.

Treatment. Rest in Bed, sodium iodid by mouth, mercury succinimid intramuscularly.

Blood-pressure in Bed drops to 165/90.

Two Months Mercury and Iodid Preparation, 6 injections neo-arsphenamin 0.2 to 0.4 gram.

Hoarseness Disappears, general condition much improved.

Second Examination. No change in objective findings.

Electrocardiogram. Rate 83, sinus rhythm. Left ventricular preponderance.

x Ray of Chest. Small aneurysm of the arch, no change.

Two Months' Rest at Home on Inunctions.

Third Examination: Hoarseness and chest discomfort gone. Introspective.

Electrocardiogram. Rate 88, sinus rhythm, notched QRS complex, Lead II, left ventricular preponderance.

x-Ray of Chest: No change.

Fourth Examination: Complaints as on third examination.

Electrocardiogram. Rate 75, sinus rhythm, inverted T wave, Lead I, left ventricular preponderance.

x Ray of Chest. No change.

"The development of T wave negativity in Derivation I unfavorable (Willius).

Treatment: Rest, small doses neo-arsphenamin 0.05 to 0.4 gm. 6 injections. Quinidin 3 gr. three times daily before and after injection. Bromids.

Sixty Inunctions at Home. Returns year and three months later.

Fifth Examination: Symptoms as on third examination.

Electrocardiogram. Rate 75 sinus rhythm, aberrant QRS; Lead II slurred, Lead III notched. T wave negative. Leads I and II. Progressive myocardial degeneration.

x Ray reported negative.

Inunctions and Iodid at Home. Returns in seven months for re-examination. Has restricted his activities markedly.

Sixth Examination: Condition fair as usual.

Electrocardiogram. Rate 82, sinus rhythm. Slurred QRS II, notched QRS III. T wave negative in Leads I and II and P wave negative in Lead III. Progressive myocardial involvement. (Coronary sclerosis?) x Ray of chest. Slight dilatation aortic arch. Heart enlarged.

Fig. 679 (*Continued*).

DISCUSSION

1 In this case again, we have an illustration of the effect of ignoring an aortic murmur Had the clue been followed up and treatment pushed at the time the life insurance examiner identified the lesion, the patient life expectancy might have been greatly prolonged.

2. Note that only with considerable effort, and after negative blood Wassermann reaction had been rechecked with positive, was it possible to obtain history of syphilis, the landmark to which the practitioner too often clings in his effort to identify the underlying cause.

3. Negative and fluctuating positive blood Wassermann reactions are not rare in syphilitic vascular disease.

4. Considering this patient's condition his treatment was fairly intensive. In view of the disastrous results that may attend therapeutic overenthusiasm, especially in the too early use of arsphenamin (Fig. 706), it was vigorous treatment.

5 *Treatment was worth while from the standpoint of the patient's comfort, for it* relieved him of his hoarseness and chest pain, greatly reduced his dyspnea, and increased his sense of well-being. In physical appearance and ability to carry on some kind of remunerative work he was very much improved.

6. From the standpoint of his aneurysm it resulted in reduction in size of the sac, an unusual occurrence. In three years the lesion retrograded from the point where it was readily identified by x-ray to the point where one x-ray was reported negative, and second some months later slight dilatation of the aorta. T this extent therapy was undoubtedly of value.

7 The valuable series of successive observations by Willius, showing progressive evidence of myocardial damage as evidenced by the electrocardiogram, raises the question as to whether the myocardium can be reached by treatment, whether progressive coronary sclerosis occurs as the result of, or in spite of, treatment, and whether the myocardial damage is the result of actual progress of syphilitic lesion, or the result of fibrosis in the process of healing. The grave electrocardiographic signs, as Willius has shown, are the appearance of T wave negativity first in Lead I and later in Leads I and II; and the development of aberrant QRS complexes.

8. It is as yet too early to evaluate exactly the influence of treatment in the development or retardation of these myocardial lesions. I another case (Fig 781) under observation for similar period, minimal treatment to arrest mild tabes with unrecognized myocardial lesion, was later found to be associated with progressive signs of myocardial degeneration, which have not yet, however terminated fatally Just what progress an untreated case could make under similar circumstances remains to be determined. There is little doubt that overzealous treatment t the outset, by inducing rapid uncompensated changes in the vascular tissues and sudden shrinkage of the coronary circulation, does harm.

and Snow (1938) at the Univ of Michigan Hospital, there were 34 per cent laborers, 22 per cent tradesmen, 15 per cent officeworkers, 26 per cent housewives or domestics, and 2 per cent professional workers.

THE PATHOLOGIC FINDINGS AND PHYSIOLOGY

The pathologic changes induced by syphilis in the vascular mechanism have been to some extent discussed in other chapters, but a review of their specific application to the heart and aorta is especially necessary to a compre-

hension of the pathologic physiology of syphilitic cardiovascular disease In the interpretation of the various changes observed the views expressed depend to some extent on the relative weight given to gross and to microscopical appearances. Thus Warthin, using the microscopical group of lymphocytes and plasma cells as a guide, stressed the enormous extent and variety of vascular involvement and gave the myocardial phase perhaps greater weight than have some clinicians and pathologists Martland for example, in the American Heart Association symposium strongly opposed Warthin's views of the importance of myocardial change in cardiovascular syphilis, stressing particularly supravalvular aortitis as the one most common and most characteristic lesion of cardiovascular syphilis. The difficulty experienced by some investigators, such as Clawson and Bell in finding spirochetes in lesions described by Warthin as spirochete-containing, has formed the basis for much argument. Personally from a number of experiences in spirochete staining and through Warthin's courtesy in allowing us to see a number of his preparations, we believe that we must yield to him as our master in the matter and ascribe to technical difficulties many of the reported failures to confirm his findings.

General Vascular Pathology.—*Spirochaeta pallida* invades larger vessel walls by way of the vasa vasorum. The endarteritic process which they set up in the blood supply of the vessel walls and the effect of the lymphocyte-plasma cell invasion is to cause patchy destruction of the elastica with crinkling, fibrotic weakening of the vessel wall and aneurysmal changes. In the finer capillaries of the peripheral circulation, as in the brain, endarteritis leads to thrombosis and ischemic injury of the affected tissue. While much emphasis has been placed on the mesaortitis associated with the involvement of the vasa vasorum, there is strong ground for the belief that an adventitiitis, or even a periarteritis, may furnish the primary source of damage, particularly in the case of the aorta and the great vessels in the mediastinum.

Pathologic Changes in the Aorta.—The bulb and lower portion of the ascending aorta is the theater for the most striking and characteristic pathologic changes in syphilis of the vascular system. Here the perivascular invasion assumes considerable importance. Klotz has pointed out that there is good reason for suspecting that the distribution of spirochetes in aortic disease is lymphatic from without, rather than hematogenous from within. The important lymph node groups in the mediastinum lie around the base of the aorta and the bifurcation of the trachea, and lymph nodes are also numerous in the mediastinal tissues. The inflammatory processes which underlie aortitis and aneurysm, therefore, are in part periaortitis and mediastinitis by extension from the lymphatic reservoirs of spirochetes in these regions as well as a mesaortitis from invasion by way of the vasa vasorum. Clinically there seems to be much to support Klotz' view of an extra-aortic factor in aortitis. The symptoms of aneurysm, for example, judging especially by their response to treatment without change in physical signs, are clinically in part those of mediastinitis and not merely those of pressure from dilated vessel whose walls have been weakened by arteritis. The symptoms may disappear without visible change in the caliber of the vessel. The pain lacks the pulsating character to be expected in mere pressure phenomena. Moreover the expansile impulse is frequently lacking in an aneurysm until after treatment has produced resolution of the incarcerating mediastinitis. Such late appearance of pulsation with relief of symptoms in spite of frequently apparent enlargement of the aneurysmal sac seems due more probably to resolving inflammatory infiltrate than to resolution of clot or of changes intrinsic to the vessel walls. The presence of enlarged lymph nodes around the ascending portion of the arch and evidence of thickening, shown by the roentgen-ray are too common observations to be entirely without significance Increase in definition of the margin of an aneurysmal sac and decrease in density which we have several times observed after treatment, seem to confirm our impression (Fig. 707) that treatment relieves symptoms in part by resolving an external inflammatory process.

The localization of the syphilitic invasive and degenerative process to the region of the aortic bulb and sinuses of Valsalva presents double menace. Infiltration with subsequent fibrotic replacement of elastica results in weakening of the aortic ring and destruction of the mobility and competence of the valve flaps. The development of nodules and infiltrates contributes to the insufficiency Martland places the site of onset of the characteristic syphilitic supravalvular sclerosis in the portion of the aorta above base line drawn through the upper limits of the attach-

ments of the aortic cusps. Utilizing the observation of Von Glahn on high-placed coronaries as frequent congenital anomaly Martland thinks that the sinuses of Valsalva are less often involved than has been believed, much of the atresia and stenosis of coronary orifices arising in the case of congenital upward displacement of the openings. There is general agreement that most of the injury done to the coronary arteries by syphilis is secondary to the aortic change about the orifices rather than in the walls of the coronaries themselves.

The Mediastinal Factor in Early Aortic Physical Signs.—The mechanism of the earliest physical signs of aortitis (accentuation and change in timbre of the second sound at the aortic area, and aortic systolic murmurs) may be interpreted as a function of the perivasculitis and mediastinitis described as early features of the pathologic process.

The experiments of Reid in the production of murmurs in tubes in which change in material or density takes place at given point bear out the possibility of murmur arising simply from change in the structure of the aortic wall and its surroundings. The fact that even a tremendous

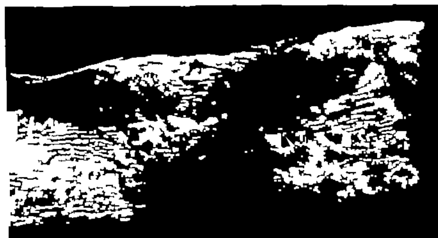


Fig. 690.—A typical syphilitic aorta. Note the criss-cross striation or wrinkling This aorta was found in patient aged sixty-five, ho was known to have had neurosyphilis during life, but in whom there had not been the slightest clinical sign of aortitis. He had been under observation and repeated examination for years.

roughening and distortion of the inner surface of the aorta from syphilitic atheroma, as shown in Fig. 690, may never produce signs marked enough to attract clinical attention, is apparent from the cases which are not recognized before necropsy These cases seem to bear out Reid' experimental observation that mere roughening of the inner surface of the tube without change in its material, rigidity or caliber does not give rise to murmurs. Leiby Callaway and Fleming (1940) suggest that the murmur is in part due to venturi effect producing eddies t the periphery of the central column of ejected blood in the dilated aorta, and the tympanitic sound to water-hammer effect from the larger volume of blood in the dilated inelastic aorta. The early signs of aortic syphilis, then, are conceivably due to the recoil of the valve and vibrations in the wall of tube whose behavior under moving column of fluid has been altered by changes in its rigidity and caliber, due to surrounding inflammatory process, periaortitis as well as an arteritis. If the periaortitis has progressed beyond certain point, damage has been done to the vessel wall and its supports which will never permit the tube to regain its normal elasticity or caliber

Treatment, with healing sclerosis exaggerates (Fig 719) rather than reduces the signs. On the other hand, if the process is extremely early function

may be completely restored and the murmur at least will completely disappear

The Mechanism of Development of Aneurysm.—The important part played by perivasculitis and mediastinitis in the development of aneurysms, especially in the thorax, is suggested by the fact that two lesions of the arch of the aorta in many respects similar as judged by clinical signs, give rise to two widely different groups of symptoms, one of which suggests a marked and severe grade of mediastinal pressure and extensive involvement, though little or nothing can be seen with the roentgen-ray while the other with a practically asymptomatic course, has a lesion easily visible by roentgen-ray. The smaller sacculations or "finger" aneurysms (Fig. 893) are of course, the results of localized bulging at weak spots due to the fibrosis resulting from inflammatory changes around the vasa vasorum, but clinically the behavior of the wholesale bulge of the whole side of the vessel as in aneurysm impresses one as more suggestive of a perivascular than an intramural lesion. This impression is deepened by observing the way in which the subjective symptoms and some of the signs of aneurysm may disappear completely under treatment, without any detectable change in the size or pressure-producing capacity of the lesion.

Study of the relations between the blood pressures of patients with aneurysm and those with aortitis alone in the Mayo Clinic material strongly indicated that the production of aneurysmal dilatation in the diseased aorta is not the direct result of the sharp, repeated pounding of a powerful hypertrophied left ventricle, producing a high but transient systolic pressure against a weakened vessel wall. The tendency of systolic blood pressure in both aortitis and aneurysm, as Martland has also observed, is to be low and especially low in aneurysm. On the other hand, diastolic pressure, presumably maintained in part by the integrity of the aortic valve, tends to be low in aortitis without aneurysm and high in aneurysm. It appears, therefore that the integrity of the valve, by making possible the maintenance of a constant, even though lower pressure on the aortic wall, is the more probable factor in deciding whether a diseased aorta will tend to develop aneurysmal dilatation or not. If aortic valvulitis is the principal feature of the picture, the patient tends to escape aneurysm by the development of regurgitation. He reaps little benefit thereby however for he is only precipitated then on to the less kindly lap of myocardial failure from atresia of the coronary orifices, coronary sclerosis, and the ultimate decompensation of a hypertrophied but inadequate or fibroid myocardium. These considerations are of some use in interpreting the treatment and prognostic outlook of the two principal types of syphilitic aortic disease.

The Myocardium.—Myocardial direct invasion by *Spirochaeta pallida* is logically a feature of all aspects of cardiovascular syphilis. Nowhere is the difference between invasion and reaction better illustrated than in the vast numbers of organisms that may be present in the heart muscle of the prenatally syphilitic child without the slightest sign of tissue reaction. But when it comes to the interpretation of the visible changes of chronic fibrotic myocarditis, the logical sequel of reaction to *Spirochaeta pallida*, discordant opinion at once becomes manifest. The inability of many in fact most pathologists, to demonstrate the organisms in heart tissue in association with myocarditis plus syphilis, has thrown much doubt about the statistical prevalence, not to say the actual existence of such an entity as syphilitic myocarditis. For an excellent critical review of the whole problem since Warthin's publications, see Saphir O Arch. Path. 16 00–15? 1933 with a bibliography of approximately 400 titles. For excellent microphotographs, see Warthin, J C J A.M A. 108 109 1937 The gist of the matter would appear to be this. Did Warthin see *Spirochaeta pallida* or artefact? Are there not reasons for suspecting that the form of the organism may be altered under conditions prevailing in heart muscle? Are the observed changes, especially the degenerative ones observed in the heart muscle of the syphilitic not equally well explained by the ischemia produced by disease at the coronary orifices, where as in the aorta, it is much easier to find acceptable *Spirochaeta pallida*? That there is a true syphilitic myocarditis seems reasonably established, in the form of an acute or subacute process, relatively uncommon in the opinion of many clinicians and pathologists. It is the ubiquity of syphilitic myocarditis that is questioned, and the specificity of changes which can be explained without the presence of spirochetes, as expressions of general myocardial injury of nutritional origin. As we have already said, our experience with the staining of *Spirochaeta pallida* in the nervous system and our observation of the striking effect of direct instruction by Warthin, on those who have had difficulty with his methods, as well as our study of Warthin's own slides, lead us to accept his belief that true syphilitic myocarditis of chronic type organism present, does exist. As the methods for the detection of conduction defect for example improve (Wolferth, Edeiken, Margolies) they indicate an increased frequency in syphilitics, but whether this increase is due to lesions or disturbances produced by ischemic fibrosis or active spirochete-containing foci, is still "over the horizon

Ischemic fibrosis of the myocardium from coronary obliteration appeared in Carr series in less than 10 per cent of 127 cases. Warthin found active syphilitic lesions of the larger coronary vessels to be infrequent. On the other hand, in contrast to the rarity of thrombosis, sclerotic changes are more frequent.

Syphilis and Arteriosclerosis, Especially Coronary Sclerosis.—Herxheimer in his discussion of syphilitic aortitis, points out how rapidly especially with advancing years, the characteristic picture of aortic syphilis is cloaked by an advancing arteriosclerosis, leading to marked fatty changes, atheroma and calcification. Scott has pointed out that syphilis gives rise t the smooth plaques which rarely ulcerate, while ulceration is common occurrence in arteriosclerosis and atheroma. Elliott has emphasized on the other hand, the comparative rarity of calcification in the syphilitic aorta. Herxheimer emphasizes the importance of comparing the root with the peripheral portions of the aorta, for in the latter the pure atheromatous changes can be identified as basis of comparison with the mixed picture presented at the root. The practical importance of arteriosclerotic change is greatest with reference to the coronaries. Clinicians, including Levine, have been disposed to assign syphilis minor role in the production of coronary sclerosis. Warthin, however in one of his last papers, reviewed this question from the standpoint of the microscopical lesions and large autopsy experience. His findings show clearly that whereas coronary sclerosis occurred in 24 and 38 per cent respectively of two groups of nonsyphilitic autopsies, it occurred in 31 and 54 per cent of the tw corresponding groups of autopsies on syphilitic patients. Angina pectoris, myocardial infarction, and coronary thrombosis likewise occurred more frequently in syphilitic than in nonsyphilitic patients.

Saphir (1933) summarized the subject of coronary embolism. Norris (1937) described in detail narrowings, puckerings, corrugations, swellings, small sacculations interspersed with yellow deposits in the first five cm. of the length of the coronary arteries, one sometimes involved without the other. *Arteriosclerosis seems to begin at the terminals, syphilis at the ostia*, but the two processes are often associated. Porter and Vaughan (1940) bring the literature of coronary embolism as complication of syphilitic aortitis up to date (30 cases, 3 new) Burch and Winsor (1942) identified myocardial infarction in 1.5 per cent of 21,618 cases of heart disease (369 cases) of which only 3 could be ascribed to syphilitic coronary stenosis. Of 103 patients with syphilitic aortitis however 40 (40 7 per cent) had narrowing of one or both coronary arteries. Strassmann and Goldstein (1942) review literature and opinion on aortic-coronary involvement.

Syphilis of Peripheral Vessels.—Clinically speaking, the circle of Willis at the base of the brain probably follows the ascending aorta in frequency as site of syphilitic vascular changes. Syphilis of the arteries of the extremities is comparatively uncommon and syphilitic thromboses and endarteritic changes in the arterioles rarer still. These processes, when they affect the larger vessels, give rise to isolated massive gangrene, and when they involve the smaller arterioles produce the remarkable picture recently described by Warthin and Wile in the form of multiple punched-out *gangrenous ulcers of the skin and subcutaneous tissue. Peripheral capillary endarteritis* gives rise to clinical pictures suggestive of Raynaud' disease and arteriosclerotic gangrene (Fig. 700). None of these pictures has, clinically at least, high degree of specificity Aneurysmal changes in the larger vessels of the extremities are well recognized, but are not always syphilitic. Saphir pointed out, from study of 80 cases of syphilitic disease of the larger vessels that the branches of the aortic arch and the common iliac, because of their excess elastic tissue, more frequently show injury and interruption of continuity of the media than do the muscular vessels such as the femoral, in which button-like fibrosis with little medial change occurs. Syphilitic phlebitis, both an acute form associated with early syphilis and more chronic type in the later stages, is well recognized, tends to involve the saphenous veins and may also affect the superficial arm veins. The literature including the earlier important contributions of E. Hoffmann, and an American case reported by Morrow and Epstein is reviewed by Evelbauer (Jadassohn Handbuch)

Gumma in the Vascular System.—Typical changes of the gummatous type occur in syphilitic infiltrates of the heart muscle (Warthin) Harlow Brooks found true gumma in 5 of 80 cases. The frequency in the case of gumma of the heart ranges according to material from 1 in 600 to 6 in 20,000 autopsies, according to Schlesinger summary (Handbuch). Spain and Johanssen (1942) summarize the experience of the Bellevue Hospital, N Y in three cases of heart gumma in which conduction defects were explained by the location of the lesion. Gordon, Parker and Soma Weiss (1942) in reporting gummatous aortitis, gave the percentage of microscopic gummas recognized in chronic syphilitic aortitis as 2.2 per cent.

Syphilis of the Pulmonary Vessels.—Syphilis of the pulmonary artery is extremely rare. According to Laubry and Marcel Thomas it may take the form of specific primary arteritis, secondary arteritis accompanying the so-called Ayerza disease (see p. 1172), and thirdly sclerotic changes. The proliferative type of arteritis with gummatous changes leads to sclerosis,

scarring and pulmonary valvular stenosis or aneurysm. (See Allan and McCracken 1940.) Warthin and Peck (1927) have discussed the pathology. McPhedran and MacKenzie have described a case of massive hemorrhagic infarction of the lung due to pulmonary endarteritis and thrombosis. Segal (1940) has reported pulmonary (gummatous) arteritis with rupture into the bronchial tree. The syphilitic character of the Ayerza syndrome is regarded by a number of observers as not completely established (Herxheimer Handbuch).

THE CLINICAL COURSE OF CARDIO-AORTIC SYPHILIS

It is customary to discuss the cardio-aortic manifestations of syphilis in terms of the structure involved. We believe, however, that a touch of vividness and a little closer contact with the examining and consulting room will be established by a chronological discussion carrying the patient from the period of syphilitic secondary manifestations through latency and the years of observational control or lapse to the actual development of clinically recognizable lesions.

The Silent Period.—We have already emphasized in previous discussions the silent invasion of the cardiovascular mechanism by *Spirochaeta pallida* and the latency ranging from several months to twenty-five or more years, when even the most thoroughgoing search fails to disclose a single abnormality. As we have already pointed out in the discussion of the treatment of early syphilis, there is a certain inevitability about the advance of cardiovascular disease during this silent period, and there are certain predisposing influences (*e. g.* physical exertion). Even under fairly thorough modern treatment for syphilis and with practically continuously negative serological tests, patients will develop the signs of the second or warning period. Relapsing serological tests, including occasional faint positives, and the fixed or irreversible positive, both should direct attention to the possibility that the silent period may terminate in definite evidence of cardiac or aortic disease.

Harlow Brooks and Carroll have observed 24 cases in which the cardiac involvement occurred during the secondary period of the disease. In 2, autopsy confirmation was obtained, the remaining 22 recovering under specific treatment. One of his patients died of acute myocardial failure, another of perforation of one of the aortic sinuses. Arrhythmia and tachycardia were observed in several instances, there were 2 cases of acute pericarditis and several of apparent early endocarditis of the aortic valve which rapidly and completely cleared up under specific treatment and no other measures. Stroud reports a case of syphilitic aortitis nine months after infection. Grassmann's study is no longer acceptable in the light of present more refined methods of study. Turner and White, in a thoroughgoing cardiovascular examination of 50 cases of secondary syphilis, including roentgenograms and electrocardiographic studies, found practically no sequelae cardiovascular changes attributable to syphilis. F. N. Wilson made physical and electrocardiographic examinations of 40 patients with secondary syphilis, with negative results. Arnett found no organic cardiovascular disease demonstrable in 25 cases of secondary syphilis, 10 with electrocardiograms by Wolferth. Arnett's study was of particular interest because it bridges the gap between the silent phase and the period of clear-cut early signs. He worked with women, in whom the incidence of cardiovascular disease is statistically less than in men, and used a control series of 70 cases which clearly brought to light the fact that until definite signs of aortitis appear (3.6 per cent of his cases, with regurgitation in 2 per cent) only a tendency to tachycardia more marked in both the early and late syphilitic patients, and an increased incidence of T-wave defects in the electrocardiogram pointed toward abnormality of the cardiovascular mechanism in the syphilitic group. Aortic systolic murmurs were no more frequent in the two syphilitic groups considered than among the controls. Lukomski found cardiac enlargement in 13.5 per cent of his cases. In contrast also with Arnett, Lukomski found definite hypertension in the younger patients, in contrast with hypotension found by Arnett. In the C.C.O. (1936) material only 10 per cent of

The Mayo Clinic series referred to in this chapter is more fully reported in the first edition of this work, and consists of 190 patients.

patients had developed detection signs before the fifth year and there was none in which the duration of the syphilitic infection was less than one year

Pericarditis and endocarditis, the former with friction rubs, has been reported (Schlesinger, Handbuch) but valvular changes with the endocarditis are skeptically regarded (Price)

The Prodromal Period.—First Warnings, Subjective and Objective.—Paradoxically speaking, of the warnings, the first may be sudden death.

Fatal Exacerbations of Myocarditis.—In 1928, Warthin, still further to confound his clinical opponents on the frequency and significance of syphilitic myocarditis, reported 8 coroner's cases of sudden death due to an exacerbation or "spirochaetal crisis" in the course of latent syphilitic myocarditis. The individual patients ranged in age from twenty-five to fifty-seven years, only 3 were definitely known to be syphilitic, in 1 there was clinical suspicion of rheumatic fever and 4 presented no clinical or historical evidence of syphilis. All were apparently in good health, the fatal accident being brought on apparently by overexertion and heat. Death occurred within few hours to two days with symptoms of dyspnea, cyanosis, vague precordial distress and dizziness, radiating pains, burning sensations, and palpitation and collapse. *Spirochaeta pallida* was demonstrated in the heart muscle of all 8 cases.

In the discussion of these cases, Warthin brought out in classic fashion his conceptions of the mechanism of cardiac death in the syphilitic patient, including: (1) Myocardial atrophy and fibrosis due to slowly progressive mild syphilitic lesions in the myocardium terminating in acute dilatation, (2) syphilitic lesions of the coronaries, resulting in infarction and fibrosis; (3) combinations of these two processes; (4) true aortic valvular syphilis with decompensation, (5) combinations of myocardial syphilis and syphilitic mesaortitis, and (6) acute myocardial death of the type just described, the frequency of which remains to be determined.

In his subsequent examination of the question of sudden cardiac death in the syphilitic patient in particular connection with coronary sclerosis, Warthin found that sudden death due to cardiac decompensation and dilatation is five times as frequent in latent syphilitics as in nonsyphilitic persons.

Prodromal Period.—First Signs of Aortic Disease.—Moore Danglade and Reisinger's effort (1932) coordinated with the work of Carter and Baker (1931) to place a well-defined symptomatology of uncomplicated syphilitic aortitis at the disposal of the physician, has resulted, first, let us say as syphilologists, in a valuable rise in the index of suspicion as applied to the diagnosis of syphilitic aortitis, and secondly in a critical and at times controversial reexamination of the entire question of diagnosis in aortitis at large, and syphilitic aortitis in particular The reexaminations have compelled substantial modification of the Moore, Danglade and Reisinger diagnostic criteria, and cannot be regarded as yet as settled In other words, there do not exist absolute criteria for diagnosis, but rather suspicion-arousers which will, and have already led to a substantial reduction in the rather discreditable gap between clinically diagnosed aortic syphilis and the prevalence of the condition at autopsy Fig 681 undertakes to summarize these suspicion-arousers under the categories of signs and symptoms, following a categorical statement of the question at issue. The individual signs and symptoms merit additional comment, as follows

The Altered Aortic Component of the Second Sound.—Agreement seems so far general that this is the most important of the early signs of syphilitic, as distinguished from general, aortitis, that every physician called upon to check the course of the disease in patients over a period of years should familiarize himself with it. It should be emphasized that altered tonal quality rather than mere accentuation is the essence of the matter The words used to describe the musical quality of the sound vary from the hollow tap of an Arab drum to the German "clang" "Amphoric" is often used, and "tambour

is to our minds the best term Age, and the absence of hypertension are essential considerations when this sound is recognized but notwithstanding this qualification, the tonal quality described gives support to a diagnosis of syphilitic aortitis. Some cases of hypertension arteriosclerosis without hypertension and some normals may give an identical tambour type of sound according to Wolferth *et al.* (personal communication)

Fluoroscopic and Teleroentgenologic Criteria.—These have grown steadily in importance under the evaluative process, and fluoroscopy seems largely to have displaced dependence on the teleroentgenogram at the hands of the most experienced observers. Maynard (1942) and Moore particularly maintain, that routine postero-anterior teleroentgenograms and the Vaquez Bordet measurements of aortic width cannot be trusted unless extreme values are noted In fluoroscopy oblique positions must be used and where the apparatus permits, plates should be timed to meet the movements of the heart. In all interpretations, experience on the part of the examiner is of great importance and particularly so in estimating the effects of age and of structural types and relations involving the thorax, the diaphragm and so forth. It is believed therefore that the most expert cardiologic assistance possible should be obtained for this work, and that *such items as the measurement* of the true diameter of the aortic knob should not be employed by those whose personal experience does not fit them to interpret such work as that of Roesler (1943) and publications such as those of Maynard (1942) Boharns, Hollander and Goldsmith (1942) and others A localized bulging of some part of the aortic arch particularly the ascending portion, is almost pathognomonic of syphilitic aortitis (Wolferth *et al*)

Aortic-Systolic Murmur—As in the interpretation of aortic density caliber and so forth age is of critical importance, so also with the aortic systolic murmur Physiologic systolic murmurs at the base of the heart are notable traps for the inexperienced and were found to be particularly common in women with syphilis and patients under stress (Arnett, 1920) a point which our experience confirms Variability from time to time during the examination or in successive examinations, particularly after the patient has been at rest, disappearance on change of posture, particularly on sitting up evidence of a nervously over-acting heart, are particular reasons for distrusting this sign. In persons under forty without hypertension, when the murmur meets the qualifications described under 4c in Fig 681 further detailed study is justified rather than a diagnosis of aortitis or a confirmed suspicion of syphilitic aortitis.

The Serologic Reaction.—Opinion on this point varies from a categorical insistence on an invariable one or two strong positives to establish the presence of syphilis, to the Cooperative Clinical Group s (1936) finding of only 73 per cent positives (including weak positives) and a reduction to 52 per cent in patients who had had preceding treatment and Willius s (1931) 10 to 15 per cent seronegatives in the Mayo Clinic experience. Blumgart (1930) estimated that 20 to 30 per cent of patients with syphilitic aortitis and complications have a negative serologic reaction. The interpretation of serologic tests in these cases is being increasingly complicated by the recognition of biologic false positives rather than negatives, so that clinical evidence and spinal fluid examination must often be invoked for assistance (see below)

Clinical Evidence of Syphilis.—This includes first scars and late syphilids (CCG 4 per cent skin, 5 per cent bone, 2 per cent visceral) (Figs. 702–703),

a reliable history of diagnosis rather than merely treatment, and above all, clinical and spinal fluid evidence of neurosyphilis which is present in from 50 to 70 per cent of patients with cardiovascular syphilis. Willius (1941) using Mayo Clinic experience, found 70 per cent of aortic syphilis to have abnormal spinal fluids. Other figures CCG (1936) 49 per cent, Wile and Snow (1938) 31 per cent, Levitt and Levy (1940) 28 per cent, Strond (1943) 50 per cent.

Minor Signs.—Pulsation in the first and second interspaces to the right of the sternum at the cricoid cartilage and in the suprasternal notch have been specifically mentioned by Strond (1943) and Willius (1941). Pulsations in the suprasternal notch are extremely common in hypertension with elongation of the aortic arch and are usually seen late in syphilitic heart disease (Wolferth, Margolies and Edeiken). Relative widening of retromanubrial percussion dulness has been sharply criticized since its proposal by Moore, Danglade and Reisinger (1932) and is now generally accepted as a late sign of aortic dilatation, pointing towards beginning aneurysm rather than towards uncomplicated syphilitic aortitis.

The Earliest Symptoms—Retrosternal Pain.—This rates easily as the most important complaint in patients with early aortitis. In the earliest cases it is more often paroxysmal than continuous and much influenced by exertion, but as the disease progresses, the continuous burning ache beneath the sternum becomes the more clearly defined symptom, and one almost immediately relieved when treatment for syphilis is instituted. Other causes of substernal pain or ache should be considered, such as hypertension, esophageal spasm, etc. Precordial anxiety dependent largely on exertion, is a much less trustworthy and suggestive symptom. Paroxysmal nocturnal dyspnea we place second, in deference to the prominent names in the literature attached to its emphasis, for in our experience it is rare. The onset of the dyspneic attack is dramatic, and in fact must be so to be distinctive the picture being that of a pseudo-asthmatic or cardiac asthmatic storm waking the patient who hastens to a window to get air and suffers acutely from a few minutes to a half an hour with abrupt subsidence of the symptoms followed by exhaustion. While Keefer and Resnik (1926) Carter and Baker (1931) and Moore and associates (1932) emphasize this symptom Kampmeier Glass and Fleming apparently found it to be almost as common (47 versus 50 per cent) in syphilitic patients without, as with pathologic evidence of uncomplicated aortitis (1942). Paroxysmal dyspnea, unless it be a nervous phenomenon, is produced by left ventricular failure or paroxysmal tachycardia of some form. It is nearly always a late manifestation of cardiovascular syphilis and is rarely present unless aortic regurgitation has developed. It is not an "anginal equivalent. Symptoms of diminishing cardiac reserve coming on abruptly in relatively young persons in whom other obvious cardiovascular disease can be excluded justifiably arouse suspicion, but are certainly not a definitive group of symptoms. Somewhat the same thing can be said of coronary paroxysmal pain with characteristic radiation, though again, coronary disease in relatively young persons without hypertension or premature arteriosclerosis very properly calls for confirmation or negation of the possibility of syphilis. In these hard pressed days, alcohol, coffee, tobacco, and cardiac (sympathetic?) neurosis, together with other causes enumerated under *anginal mechanisms* must be carefully weighed, and are too often overlooked.

What Makes Clinician Diagnose Rheumatic Aortic Valvular Disease as Against Syphilitic Aortitis?—The literature on this question is controversial and sometimes, within the same paper

Fig. 681

SUSPICION AROUSERS IN SYPHILITIC AORTITIS

The Close of the Latent Period

1. Existing controversy embraces the questions:
   (a) Can aortitis be definitively diagnosed before complications appear?
   (b) Can aortitis when recognized be diagnosed by direct evidence (distinctive symptoms and signs) as syphilitic aortitis.
2. The weight of opinion, broadly speaking, answers both questions with a qualified no. Uncomplicated syphilitic aortitis may be suspected rather than diagnosed
3. Among the authorities, in answer to 1a (note the "qualified" above)—
   (a) Yes: Moore (1941) Howles (1943) Stroud (1943) Hansen (1944), Maynard (1944), Carley and Reid (1942), Cooperative Clinical Group (1936), Leiby Callaway and Fleming (1940), Dressler and Silverman (1945).
   (b) No: Scott (1947), Wilson (1937) White and Wise (1937), Nichols (1940) Bedarra, Hollander Goldsmith (1942), Kampmeier Glass and Fleming (1941), Wolferth, Margolies and Edeiken (personal communication, 1943).
4. The earliest suspicion-arousing signs in order of accepted importance (more important than symptoms):
   (a) Evidence of localized aortic bulging, especially of the ascending portion of the arch; abnormal density (many uncertainties including anatomical and other variations), considering age (under forty) and medical history; abnormal or localized pulsation and bulging, especially to the right. Fluoroscopy essential, plate much less reliable (Maynard), especially Vaquez-Bordet measurements.
   (b) The altered (tympanitic, amphoric, tambour) aortic component of the second sound, in patients under forty without hypertension.
   (c) An aortic systolic murmur in persons under forty without hypertension, persistent with or accentuated by change of posture (sitting). Transmission upward into vessels of neck, occasionally heard at apex.
   (d) Clinical evidence of syphilis, including neurosyphilis, scars, reliable history etc
   (e) A confirmed positive serologic test or tests.
   (f) Pulsation first and second interspace to right of sternum or in suprasternal notch (relatively late may be due to elongation of arch as in hypertension).
   (g) Relative widening of retromanubrial dulness (late and in other conditions).
5. The suspicion-arousing symptoms (nonspecific and less significant than signs)
   (a) Retrosternal pain, precordial stress, on exertion or continuous.
   (b) Paroxysmal (nocturnal) dyspnea (rare in our experience also Wilson) Very late produced by left ventricular failure with aortic regurgitation, may be simulated by nervous phenomena (Wolferth *et al*)
   (c) Diminishing cardiac reserve: tachycardia, weakness, dyspnea and nonproductive cough on exertion, palpitation, dizziness, edema. Some late some nonspecific
   (d) Coronary (paroxysmal) pain, with characteristic radiation, etc (usually late).
   (e) Abrupt onset of above symptoms under age forty alcohol, coffee and tobacco, and rheumatic heart disease considered.
6. Electrocardiographic changes. In young persons without other explanation, may be suggestive A higher proportion of EKG abnormalities in syphilitics without physical signs of heart disease than in similar group of nonsyphilitics. Conduction disturbances (minor intraventricular defects) T wave changes, slurring or splintering of QRS complex and so forth (Wolferth, Edeiken and Margolies).
7 Suspicion-arousing calls for due weight and examination for other causes of cardiac disease painstaking examination for evidence of syphilis; willingness to use the therapeutic test with conservative interpretation of nonspecific effects; and to be a little more ready to accept the syphilitic possibility than determined to reject it.

self-contradictory for which coverage is sought by the statement that so many exceptions exist that categorical statement is impossible Even on the question as to whether syphilitic and rheumatic aortic valvular disease coexist, there is no unanimity but the studies of Liss and Chandler (1934) and Liss, Solomon and Eckstein (1942) seem clearly to indicate that coincidence of the

two diseases is not rare. Wolferth, Margolies and Edeiken have given us (personal communication) a summary of the more usable differential criteria as follows

1. Age.—Rheumatic insufficiency develops early in life, rarely after thirty years of age except in connection with an undoubted attack of rheumatic fever in an adult (the mild attacks are confined to childhood).

2. Nonprogressive lesion.—In syphilitic, untreated, a nonprogressive lesion points toward rheumatic disease.

3. Dilated Aorta (localized bulging).—Though sometimes present in young persons with rheumatic heart disease, the dilated aorta suggests syphilis, especially before regurgitation appears.

4. History of Rheumatic Fever.—If positive, suggestive of rheumatic aortic valvulitis. If negative, and with previous negative heart examination, suggests syphilis.

5. If serologic tests negative but aorta dilated, in the absence of history of rheumatic fever the process is syphilitic until proved otherwise.

6. A coincident mitral lesion tends to support diagnosis of rheumatic aortic valvular disease.

7. Aortic stenosis may develop where syphilis and rheumatic fever coexist (anatomically or clinically) but aortic stenosis swings the diagnosis toward rheumatic fever. Progression after long latency suggests but does not prove syphilis. Many provisos.

8. Aortic diastolic murmur transmitted down right side of sternum with dilated aorta, suggests syphilis.

Other informative discussion includes Nichols (1940) who mentions especially the low reserve and short life of the victim of syphilitic aortic disease after regurgitation develops, in contrast to the benignity of the rheumatic lesion. An important group of papers includes Braunstein and Townsend (1940), Rosenberg (1940) and Koletsky (1940) on the coincidence of syphilitic aortic valvular disease and bacterial endocarditis. Koletsky emphasizes the importance of using autopsy evidence alone in establishing such coincidences, point the more significant with the newer developments on biologic false positive serologic tests.

In the Mayo Clinic series, taking sixteen years as the mean duration of infection, it was evident that very much larger proportion of cases of aortic and particularly valvular damage are recognized early than of aneurysm.

The Third or Progressive Period.—The progressive period carries forward the signs and symptoms of the prodromal period and ends in the parting of the ways, so to speak, between aortic regurgitation and aneurysm (Fig. 687). From the Mayo Clinic study it was possible in this phase to differentiate the

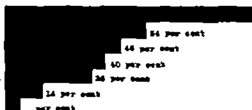


Fig. 688.—Interrelations of cardiovascular and neurosyphilis.

pain of simple aortitis with its frequently anginoid character from the more continuous aching, grinding, or neuritic pain of an aneurysm. Our survey of the diagnostic problem in this stage showed clearly how essential it will be if we are to accomplish a fundamental advance in our diagnosis of cardiovascular syphilis from the standpoint of preventive medicine to carry our conceptions of its earliest onset well back of the period of obvious physical signs described in the text-books. The first step in achieving an adequate index of suspicion is to realize that latent syphilis may be present in every patient who consults us. This implies a systematic inquiry into the history of sexual habits and possible infection, regardless of the social status or personal make-up of the patient. Yet in our cardiovascular survey this was lacking in a fifth of

the cases. It was evident that serological tests must be applied routinely in all medical examinations if they are to be of genuine service in the prevention of cardiovascular disease. A much more thorough physical examination than is often given is essential in the critical scrutiny which prevents vascular disease from emerging from the latency of an unrecognised syphilis. Attention will presently be drawn to the early signs of neurosyphilis most important in our experience and emphasized also by Moore Danglade, and Reininger in detecting syphilitic cardiovascular disease while it is still in a treatable stage. Had the knee jerk been interpreted rather than merely recorded in Fig 721 the tabes would have been considered and treated perhaps in time to forestall



Fig. 683.—*Treponema pallidum* in heart muscle. Stained by Levaditi method (× 1000) (Collection of Dr Noguchi.)

the appearance of cardiac degeneration. Had it occurred to someone that gumma and sarcoma of the testis are constantly confused treatment might have been of some help (Fig 719) Insistent and repeated warning that reliance on the patient's story and treatment based on his presenting symptoms will let early vascular syphilis slip through must be dinned into the ears of the coming generation of physicians. The moment syphilis comes above the etiologic horizon in a given case, the patient's name should be placed on a pad calendar so to speak, like that of an obstetrical patient and his vascular system should be subjected to reexamination by a competent observer at intervals throughout life

It is well, too, in this stage to comment on the influence of age in connection with the symptoms. While the age of the patient undoubtedly influences any estimate of the importance of the various clues the mere fact that a patient is more than forty five years old when signs appear should not lead to too hasty a conclusion that causes other than syphilis underlie his vascular lesion. It is well, we believe slightly to overemphasize rather than under emphasize the syphilitic possibilities in the so-called "pseudo anginas" and the "neurotic hearts," which have never really been completely evaluated from the standpoint of modern syphilology Every syphilitic patient with an irritable" heart or precordial stress and pain, even though repeatedly negative serologically can be seriously considered as a candidate for a therapeutic test or if not that, at least for thoroughgoing annual study The inclination



Fig. 694.—Aneurysm of the descending aorta. This type of lesion produces the posterior dulness in percussion along the spine.

to diagnose "neurasthenia" or "menopause" whenever the symptom complex becomes a bit baffling is entirely too easy to be safe for the patient (Fig. 693) or satisfying to the physician when subsequent events demonstrate the underlying cardiovascular syphilis.

Toward the close of the progressive period the recognition of a faint diastolic whiff appearing at A_2 marks the beginning of regurgitation, if it is to develop, while the transition into diastolic shock and the appearance of thrill marks the development of well-defined aneurysm. It is at this point that the much-debated roentgenological signs are put forward with increasing confidence by their proponents. Let it be emphasized, as Willius, Thayer Conner and others have maintained, that the diagnosis must rest upon the broad and well-coordinated interpretation of the entire case.

Roentgenological Diagnosis of Early Aortic Syphilis.—Moore, Danglade, and Reisinger's table (Fig. 686) from their careful survey rates roentgeno-



Fig. 685.—Aneurysm of the descending portion of the arch of the aorta.

logical evidence of aortic dilatation first among the criteria they consider useful in the diagnosis of uncomplicated syphilitic aortitis.

Fig. 686.

THE INCIDENCE OF VARIOUS SYMPTOMS AND SIGNS IN PATIENTS WITH SYPHILITIC AORTITIS PROVED AT NECROPSY
(From Moore, Danglade and Reisinger.)

	Total cases with information available.	Number of patients showing symptom or sign.	Percentage.
History of circulatory embarrassment	88	44	50.0
Widened retrosternal dullness	89	44	49.4
Accentuated tympanitic A2	90	23	25.6
Roentgen evidence of widened aorta	29	25	86.0
Paroxysmal dyspnea	90	7	7.7
Pain	80	14	17.9
Cardiac failure (not terminal)	92	24	26.0

In the American Heart Association symposium Steel, Kurtz, and Eyster and Hampton, Bland, and Sprague of the Massachusetts General Hospital, summarized present views of the

problem and created much discussion among the clinicians. Steel named five changes as associated with the pathologic aorta, as follows:

1. A dense shadow often with hazy borders.
2. A high, dense, and prominent aortic knob.
3. Irregular and also general dilatation.
4. Increased pulsation.
5. Association with aortic insufficiency

Of these, he rated irregular dilatation as the most important, particularly spindle-shaped dilatation of the root. This change causes the anterior and posterior borders of the ascending aorta to run, not parallel as normally but to converge toward the high aortic knob, giving the silhouette triangular appearance with the base down. Kurtz and Eyster named as criteria for diagnosis of aortitis the following:

1. Elongation or tortuosity
2. Widening of any portion.
3. Pulsation to the right of the sternum.
4. Increased density permitting visualization of the descending aorta, especially in patients under the age of fifty years.

It was conceded that it would ordinarily not be possible to distinguish between the syphilitic *and arteriosclerotic types of aortitis by fluoroscopic examination.* The Massachusetts General Hospital group discussed interpretation on the basis of the Hampton and Jones technic of oblique teleroentgenological examination of the aorta. The interpretations depend upon careful measurements of aortic dilatation; the normal and arteriosclerotic ascending aorta without dilatation averages 5.5 cm. while the dilated ascending aorta invariably measures over 6 cm. in diameter when estimated by the method presented. None of the roentgenological methods undertakes to do more than to assist in the identification of aortitis, the etiologic factors responsible for the condition being decided by clinical, serological, and other roentgenological findings.

In the literature since 1934, the above criteria have largely been reiterated with emphasis on their inability to stand alone. The angulation of the aorta in oblique roentgenography (Nichols) and the localized bulge repeatedly stressed by Wolferth and coworkers seem important, but nihilistic views are expressed by Bohares, Hollander and Goldsmith.

The Period of Consequences.—Figure 687 is drawn to illustrate schematically the offshoots from the stage of uncomplicated syphilitic aortitis which in the form of aortic regurgitation, coronary disease, and aneurysm constitute the picture of late consequences terminating in myocardial failure or rupture, and death. It will be recalled that it is essentially the preservation of the integrity of the valve with its maintenance of aortic diastolic pressure that would *seem to furnish the force back of* the aneurysmal bulge of the weakened aortic wall. There is a tendency to low systolic and high diastolic blood pressure in aneurysm and relatively the reverse in aortic regurgitation. Figure 688 compares the subjective symptomatology of syphilitic aortitis with that of aneurysm Kampmeier's observations on 566 cases of aneurysm show relatively similar proportions. The symptoms of aortitis are distributed more evenly over the range of cardiac and circulatory embarrassment with pain, dyspnea, palpitation, and indigestion leading the list, and hoarseness, so prominent in all thoracic aneurysms, almost never occurring in aortitis. In watching cases clinically both before and during treatment, one is impressed with the great significance of precordial distress and dyspnea as early warnings of cardiac and aortic lesions in general and with the fact that they may long precede the development of signs. While this may seem a truism it by no means finds the application in practice that it should. A complaint of shortness of breath or precordial stress, even if not actual pain, should not be dismissed as due to neurasthenia or overweight.

The Signs of Aortic Regurgitation.—The progressive nature of the process is expressed in the developing signs. Both symptoms and signs are summarized in order of frequency in Nichols (1940) and Kampmeier's (1943) published

Roentgenological Diagnosis of Early Aortic Syphilis.—Moore, Danglade, and Reisinger's table (Fig 686) from their careful survey rates roentgeno-



Fig 685 —Aneurysm of the descending portion of the arch of the aorta.

logical evidence of aortic dilatation first among the criteria they consider useful in the diagnosis of uncomplicated syphilitic aortitis.

Fig. 686.

THE INCIDENCE OF VARIOUS SYMPTOMS AND SIGNS IN PATIENTS WITH SYPHILITIC AORTITIS PROVED AT NECROPSY

(From Moore Danglade and Reisinger)

	Total cases with information available.	Number of patients showing symptom or sign.	Percentage
History of circulatory embarrassment	88	44	50 0
Widened retrosternal dulness	89	44	49 4
Accentuated tympanitic A2	89	25	28 1
Roentgen evidence of widened aorta	93	25	26 9
Paroxysmal dyspnea	90	7	7 7
Pain	89	16	17 9
Cardiac failure (not terminal)	92	24	26 0

In the American Heart Association symposium Steel, Kurtz, and Eyster and Hampton, Bland, and Sprague of the Massachusetts General Hospital, summarized present views of the

experience in Fig. 689 Functional diastolic murmurs are said by Wilson to occur occasionally but as a rule they are of structural origin and according to Wilson practically indicative of syphilis.

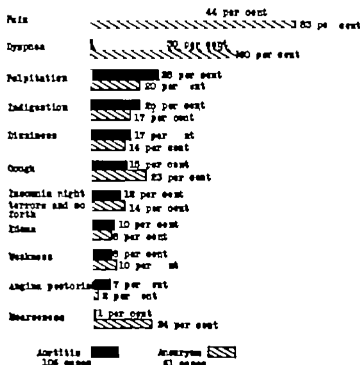


Fig. 688.—Comparative symptomatology of aortitis and aneurysm.

The loud musical diastolic murmur is due to retroversion of the right anterior valve flap (Bellet, Gouley Nichols and McMillan 1939) or rupture of leaflet. Blackford and Smith (1936) do not consider diastolic aortic murmur diagnostic of syphilitic aortitis in the Negro.

Fig. 689.

SYMPTOMS AND SIGNS OF AORTIC INSUFFICIENCY

Symptom or Sign	Nichols (1940) (70 cases) %	Kampmeier (1943) (163 cases) %
Aortic diastolic murmur	100	100
Definite cardiac enlargement	83	
T and fre murmur	87	
Dyspnea on exertion	71	74
Edema	40	47
Corrigan pulse	80	47
Cough		45
Austin-Flint murmur		15
Pain (cardiac) or substernal oppression	43	41

The insufficiency arises primarily from the widening of the commissures between the valve flaps, whether due to fibrotic weakening and dilatation of the ring or as Scott maintains, to the adhesions of the margins of the cusps

to the aortic wall, a pathologic picture which is stated by Scott to be pathognomonic of syphilitic aortitis. Cardiac enlargement and hypertrophy invariably occurs at this stage and the heave which this increase in size and effort requirement imparts to the precordium can often be recognized almost across the room as the heart attains the proportions of the *cor bovinum*. The left ventricular hypertrophy can be early recognized also in the roentgenogram. Diminution of the aortic second sound, or its complete overshadowing by the diastolic murmur, not infrequently occurs and its decreased audibility or absence in the vessels of the neck is a point in favor of aortic insufficiency (Thayer). The "blubbering" or rumbling Austin Flint murmur presystolic at the apex, was recognized by Carter and Baker in 50 per cent of their cases, and in 4 patients was associated with a palpable thrill at the apex. The differentiation of this murmur from that of mitral stenosis in the presence of a history of rheumatic disease is fully discussed by Thayer. Carter and Baker

Fig. 600.

IMPORTANT CONSECUTIVE SIGNS IN THE COURSE OF THORACIC ANEURYSM	
Accentuated A_2. All other heart sounds may be normal	**Asynchronism of Radial Pulses:** Absent pulse in one arm.
Signs of Aortitis of Varying Degree M y or May Not Be Present.	**Differences in Blood-pressure** between the t arm
Precordial Dulness t various points bove the base of the heart if aneurysm is of the arch.	**Signs of Mediastinitis** Fulness of neck veins, flushing, lividity on stooping or lying down, retarded *venous return*, etc.
Dulness Posteriorly but less sharply defined, if aneurysm is of the descending orta	**Inequality of Pupils** (small, but reacting to light on ffected side) *Distinguish from Argyll Robertson pupils.*
Absent or Impaired Breath Sounds over the dull area.	**Conspicuous Ray Signs of Tumor,** *with or without pulsation* hen seen fluoroscopically
Fluoroscopic Pulsation Plate show dilatation or neurysmal shadow	**Thrill and Diastolic Shock.**
Systolic Bruit Over the Dull Area (may be absent)	**Tracheal T g.** (Aneurysm of the arch)
Systolic Impulse, Upper Thorax, palpable or faintly visible. May ppear in supraclavicular region or neck. Ma be visible posteriorly above the scapula or close to the vertebral column in involvement of the descending aorta.	**Visible Tumor** heaving or expansile pulsation.
Paralysis of One or Both Vocal Cords with or without Hoarseness.	**Physical Signs from Erosion Into Neighboring Structures.**
	Sudden Death from Rupture.
	Signs of Cardiac Failure from progressive coronary sclerosis, *aortic regurgitation* or myocarditis.

were unable to confirm Herrmann's suggestion that this murmur is produced by major involvement of the posterior aortic cusps, and Gouley (1911) believes it due to the vibrations of a cupped or pouched aortic flap.

Certain symptoms and signs have negative value in that their absence strengthens the diagnosis of late syphilitic aortic disease. Carter and Baker and Nichols mention the absence of evidence of mitral *disease as* important in eliminating rheumatic fever. The absence of auricular fibrillation, commented upon by a number of writers, including Willius and *Carter* and Baker, is given by the latter almost the weight of an excluding element in diagnosis. Syphilis was present in only 3 per cent of their large series *of auricular fibrillations*, the proportion being much higher in rheumatic and arteriosclerotic heart disease (85 per cent). Fever, mentioned by Reid as *occurring in a number* of his cases, was notably absent in the Mayo Clinic series and in that of Carter and Baker.

The current literature of aneurysm includes several reports based on large material, notably the excellent study of Kampmeier (1938) and the CCG series (1938) which contain interesting statistical data but have not altered the main outlines of the subject, of which this text is representative. Kampmeier defines the pain of aneurysm as present in 60 per cent of the transverse and ascending arch groups, in 78 per cent of the descending arch and 86 per cent of the descending thoracic portion. Dysphagia, vertigo, tracheal compression and hoarseness are more common in transverse arch involvement. Another group of reports concerns itself with unusual aneurysmal localizations; Kampmeier abdominal aneurysms (1936), hepatic (Malloy and Jason, 1940),

Fig. 691.

HOARSENESS AS THE FIRST SYMPTOMATIC WARNING IN ANEURYSM OF THE ARCH. INCREASED BASAL CARDIAC DULNESS AS AN EARLY PHYSICAL SIGN. ABSENCE OF MURMURS

Locomotive engineman, aged thirty-eight years, married.

Examined July 13, 1918.
Chief Complaint: Hoarseness.
On questioning it was found that he had been short of breath and had smothering spells for eight months.
Penile Sore Twenty Years Before. N secondaries.
Treatment Mercury and potash by mouth. Fifty rubs in three courses at Hot Springs. Medication by mouth, off and on, since. Recently 4 injections of arsphenamine and further treatment by mouth.
Preventive Test Negative Five Months Before Examination.

Examination (Laryngology) Complete paralysis of left true and false cords.
Ray of Chest Mediastinal tumor aneurysm, aortic arch.
Physical Findings (Willius)
Heart 4.5 by 10, apex eighth interspace.
Increased basal and cardiac dulness, 9.5 cm. wide over upper sternum.
A arrhythmia, no murmurs.
Faint tracheal tug.
Blood-pressure 98/74, 98/72, both arms.
Electrocardiogram, rate 90, sinus tachycardia.
Blood Wassermann Reaction: Strongly positive
N Change Occurred Under Treatment.

Discussion

1 This is typical example of "too late.
2. It is also an excellent illustration of the ineffectiveness of much that has passed as treatment for syphilis in the prevention of vascular accidents. This man had had almost lifelong treatment of one sort or another, but always inadequate.
3. A negative preventive test means little or nothing in the future course of case.
4. Gummatous mediastinitis and sarcoma, substernal goiter mediastinal Hodgkin' and malignant metastasis must all be considered here.
5. There was curious traumatic history in this case that may or may not have been significant. He was beaten about the neck daily with "hammer for four minutes three times day as part of his previous treatment.
6. Involvements of the recurrent laryngeal nerv are most frequent in aneurysms of the ascending and transverse portions of the arch. A very large tumor toward the descending limb may give no symptoms.
7 A thoracic examination consisting merely of auscultation might have missed the lesion completely
8. Note that the valve (aortic) is apparently intact. There were no signs of acute dilatation.
9. Reduction in the size of an aneurysm is rare under treatment.

celiac (Lalpply 1945) Rupture of an aortic aneurysm into the pulmonary artery (Potter 1934, rated 54 reported cases as authentic) has definite syndrome including continuous and severe breathlessness; preponderance of right heart failure of early onset; slight pulmonary stasis not proportional to dyspnea, cyanosis is present; purring systolic and diastolic thrill over base; long harsh continuous murmur loudest at left 3d interspace no Austin Flint; roentgenogram shows aneurysm of ascending aorta. (Other reports include very complete summary by Nicholson, 1943.) Welty (1939) demonstrates the decline in the frequency of aneurysm from 23 per thousand autopsies to 9.5 per thousand from 1907 to 1937

The Signs of Aneurysm.—In this field the Mayo Clinic material was particularly instructive (Fig. 690) Probably the earliest clinching identification

Fig. 602.

THE SYMPTOMS OF MEDIASTINITIS AND ANEURYSM OF THE ARCH CONFUSED WITH NEURASTHENIC AND HYSTERIC SYNDROMES. UNSUPPORTED POSITIVE WASSERMANN REACTION ON PROVOCATIVE TEST. CONFIRMATION BY THERAPEUTIC TEST

Housewife, aged thirty-three years.

Examined February 17, 1918.
Chief Complaint. Flushing and choking sensations of two years' duration.
Extremely nervous.
Feels as if a string were drawn tight around her neck.
Face "bloats" on slight exertion.
Much worse on lying down.
Lips get blue at times she said.
Said also that hands and feet bloated.
No obstruction to respiration, but slightly short of breath on exertion.
Occasional slight precordial pain.
Could not raise arms over head without their getting numb.
One Miscarriage. One Healthy Child.
Tonsils Removed to relieve above symptoms.
Pustules on Face Two Months after Vaccination fifteen years before. Wound sore two months.
Examination (Preliminary).
Face pocked, right kidney palpable, uterus tellered.
Blood Wassermann reaction negative.
Blood-pressure 150/90. Hemoglobin 57 per cent.
Test-meal negative.
Examiner's Diagnosis. Neurasthenia. Secondary anemia, advise Blaud's.
This Examiner's Consultant Found the Following Additional Points of Interest in checking this opinion.

Consultant's Examination (W. A. Plummer).
Face congested. Filling of neck veins.
Left pulse nearly disappeared on raising hands above head.
Blood-pressure right arm 130/100, left, 145/100.
Orders x-Ray of Chest for Substernal or Mediastinal Growth.
x-Ray of Chest. Aneurysm of the descending portion of the aortic arch.
Syphilologist Ordered Provocative Procedure to check the negative blood Wassermann result.
One Strong Positive Test. Six negatives.
Treatment Continued. Six arsphenamin *injections.*
Felt Much Better. Could now stoop, and dress her hair without trouble with arms. Throat better, no palpitation, no edema of face.
Spinal Fluid Negative.
Took 20 Injections at Home.
Returned "In Wonderful Shape." Practically nothing left of her original symptoms except some palpitation on exertion. Sleep, nervousness, and so forth, all better.
x-Ray Showed No Change in Aneurysm.
Patient Lapsed from Observation After Three More Arsphenamin Injections. Considered herself well.
She Had Never Had but the One Positive Blood Wassermann Reaction in Eighteen Months' Observation.

DISCUSSION

1. To the hasty, snap-shot, subjectively minded physician, who eliminates syphilis by the negative blood Wassermann examination and no history, this might well sound like the story of a nervous, hysteric woman.

2. Careless and incomplete examinations, and the designation of neurasthenia on snap-shot impression pass an enormous amount of syphilis unrecognized through the clinics and hospitals of the country.

3. Flushed face and thumping neck do not always make a *diagnosis of menopause.*

4. Difference in blood-pressure and pulse between the two arms repeatedly give the clue to aneurysms of the arch that even the x-ray may overlook at first.

5. One of the earmarks of mediastinitis is the engorgement of the face on stooping or lying down, and the development of cyanosis almost to lividity.

6. Why so good a therapeutic result when there was no change in the aneurysm seen with the fluoroscope? Presumably this is due as is remarked in Fig. 107 to the resolution of the peri-aortitis and mediastinitis which seems always to precede or accompany an aneurysm. This infiltration and not the pressure of the aneurysm seems to be responsible for many of the symptoms. The rigidity which it imparts to many aneurysmal sacs leads to diagnoses of tumor before treatment is begun, which must be revised after the first course or two when expansile pulsation becomes apparent.

7. Patients with aneurysms seen at this stage and judiciously treated and watched have a good life expectancy.

of aneurysm or rather an impending aneurysm of the aorta and its branches is made by the fluoroscope in cases in which abnormal dilatation of the circumscribed portion of the aorta under *the systolic impulse of the heart* can be detected Physical diagnosticians very properly contend, however that broadening and distortion of the arch can be detected very early by careful percussion to the right of the sternum from the base of the heart upward. This broadening and extension upward of the percussion outline of the base *of the heart, especially when the dulness appears on both sides of the sternum* may be quite trustworthy but should always be supplemented by careful fluoroscopy It is worth while to emphasize that the earliest physical signs of aneurysm are obtained by percussion and palpation in contrast to the use of auscultation in the detection of early aortic disease. The accentuation and tonal change in the aortic second sound is not invariably present, or if it is it may be the only auscultatory sign if the root of the aorta and the valves are not involved It is for this reason that very careful percussion of both the front and back of the thorax is necessary It would seem to be the lack of percussion findings, or rather their obliteration by liver dulness that makes the subdiaphragmatic aneurysm so hard to identify in life. Percussion close to the vertebral column may yield a small area of dulness with obliteration of breath sounds in aneurysm of the descending aorta.

The late signs of aneurysm begin with pulsation and thrill. A soft systolic bruit may be heard early but the louder murmurs and diastolic shock are parts of the picture of aneurysms better suited for display in pathologic collections than for demonstration as hopeful therapeutic cases. Differences in blood pressure in the two arms proved to be important in identifying several of the aneurysms of the arch and its branches in our series.

The location and contour of an aortic aneurysm and the amount of periaortitis and mediastinitis involved provides for a disconcerting variety of symptoms and signs. For example, tracheal tug may appear quite early or very late according to the location of the sacculation of the arch. It is remarkable how nearly asymptomatic an aneurysm may be in its beginnings and how often signs, if present, may be of a type likely to escape a hasty examiner who merely auscultates without percussing (Fig. 691) or without comparing the pulse and blood pressure in the two arms (Fig 692) Bulging to the left may reach a large size with but few signs, whereas bulging to the right and upward from the same point in the arch may give rise to a wealth of signs. The subdiaphragmatic and abdominal aneurysms, perhaps because they are rarer seem to pass unsuspected until they reach a size which gives rise to radicular pressure pains. They may be more or less completely concealed from roentgenological observation by the overhanging liver The signs associated with various types of aneurysms are illustrated in the case histories, and certain important syphilological and fluoroscopical diagnostic points in Fig 693 The types of aneurysms in order of frequency are as shown in Fig. 694 Subclavian aneurysms in particular were important in our experience, 5 cases occurring in the series. The resemblance of the signs of a large innominate aneurysm to substernal goiter is illustrated in Fig 713

Pressure Signs.—The response of the so-called "pressure signs" of aneurysm of the arch such as cord paralysis from involvement of the recurrent laryngeal nerve and the vagus, pupillary inequality from involvement of the cervical sympathetic, and compression of the trachea, even when the mass *itself shows little apparent reduction in size* suggests that there is either a

disappearance of inflammatory reaction, or that the mass becomes more yielding or less pulsating and less capable of producing compression symptoms



Fig 693.—Forty-nine diagnoses of aneurysm, exclusive of aortic dilatation.

under treatment. It is perhaps for this reason that pressure signs may sometimes seem so conspicuous in comparatively small aneurysms (Fig. 695) and

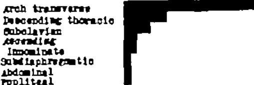


Fig. 694 —Types of aneurysms in order of frequency Kampmeier found lower proportion of transverse (32 per cent)

that large sacculations of long standing, in which the acute perivasculitis has subsided or intravascular clotting has occurred, may give rise to an amount of discomfort small in proportion to the extent of the tumor In following the



Fig. 695 — Finger type aneurysm of the aorta, perforating the trachea. Death from rupture. Symptoms those of tracheal obstruction. (Courtesy of Drs. Gabriel Tucker and Richard Kern.)

data given by patients it has often seemed that hoarseness antedated by a long period the presumptive appearance, at least, of gross signs of dilatation.

Differentiation of Mediastinal Tumor and Aneurysm—Fluoroscopic Error.—It is in the fluoroscopic differentiation of mediastinal tumor and aneurysm that the probable influence of perivascular and mediastinal incarceration of the sac in the surrounding inflammatory infiltrate reaches its greatest importance. Obviously in the roentgen-ray if any enlargement whatever is disclosed, it appears as a tumor whose location may, of course, identify it correctly. It is quite likely, however, to be indistinguishable from the lymphomatous tumors of mediastinal Hodgkin's disease or lymphosarcoma, from malignant metastasis and from substernal goiter. The crux of the roentgen-ray differentiation, therefore, rests with fluoroscopic study. But if pulsation is not apparent, the inclination is to diagnose a solid tumor (Fig. 713), occasionally allowing for the possibility of an aneurysmal sac fixed by intramural clotting (Fig. 706). Our study indicates that this point of view is distinctly fallible, and that the entire picture may be transformed by a short therapeutic test, which, by resolving the mediastinitis and perivasculitis, permits the pulsation of the "tumor" to become visible under the fluoroscope (Fig. 707).

Question of tumor cross — 19 cases

Question raised by x-ray plat — 13 case

Fluoroscope showed pulsatio on first examination — 7 cases

Fluoroscope showed no pulsati on first examination — 6 case

Total positive therapeuti tests — 6 cases

Pulsatio appeared after therapeutic test — 4 cases

Diagnosis f syphilis confirmed by disappearance f symptoms — 4 cases

Physical signs confirmed aneurysm 1 spit f negative fluoroscope — 1 case

Necropsy confirmed aneurysm — 1 case

Fig. 696.—Tumor versus aneurysm.

The technic and differential considerations when the therapeutic test is used for the recognition of aneurysm are discussed on page 937.

Enlarged Lymph Nodes May Accompany Syphilitic Mediastinitis.—It should be emphasized that the presence of palpable or even markedly enlarged lymph nodes in the supraclavicular spaces or the axilla, does not establish a diagnosis of malignant mediastinal growth or lymphoma, or render a therapeutic test for syphilis unnecessary. Gummatous local adenopathies simulating metastasis, common in the neck in association with syphilids of the throat and tonsils, must also be reckoned with (Fig. 712) in association with the mediastinitis of aortic aneurysm. At the same time it must not be forgotten that carcinoma and syphilis may be closely connected, and that examination of an accessible gland is entirely safe if treatment is begun afterward. The microscopic diagnosis on the node may indicate the uselessness of treatment except for palliation, or permit additional treatment by roentgen-ray.

Cord Paralysis.—We have been repeatedly impressed with the importance of hoarseness as a symptom for the general practitioner's attention (Fig. 691), although, especially with accompanying aortitis, pain in the chest and dyspnea were more likely to be the patient's chief complaints.

The value to the general diagnostician, working unaided, of being able to see the vocal cords, deserves emphasis, and such an examination in case of prolonged hoarseness should be made without waiting for the brassy cough. The equipment is simple; a lamp, a head mirror, large laryngeal mirror, a glass of hot water towel, and a soothing and reassuring voice may occasionally afford the physician on the frontier a most gratifying diagnostic *coup d'œil*. In fact,

Fig. 697

SYNDROME OF COMBINED TUBERCULOSIS AND SYPHILIS (?). AORTITIS WITH ANEURYSMAL (?) DILATATION IN A CHILD

Boy aged six years.

Examined March 15, 1918.

Chief Complaint: Swelling of one finger ulcer on toe, cough, tired easily Pain in back on jarring or handling

Family History Mother lost first baby from smallpox at birth. One miscarriage, two living children.

Whooping-cough two years before. Fluid in abdomen three weeks. Short of breath since influenza. Pneumonia and pleurisy Attacks of pain in abdomen.

Examination *Slight kyphos* and rigidity of fourth, fifth, and sixth dorsal vertebræ. Probably tuberculosis, but little destruction. *Proximal phalanx* left third finger spina ventosa. Sinus, great toe. Nasal bridge depressed. Liver *enlarged*, left lobe hard and nodular

Spleen palpable.

Doughy mass right iliac fossa.

Blood-pressure 98/68.

Von Pirquet tuberculin +++

Blood Wassermann reaction weak positive.

Brother's Wassermann reaction, eak positive.

x-Ray of bones, destruction of finger and toe.

x-Ray of chest, mediastinal shadow right upper

Fluoroscopic Pulsation, aortic dilatation. Spine negative.

Consultant's Opinion: "History of ascites with indurated left lobe liver may mean former tuberculous peritonitis, or ith dilatation of aorta may signify syphilis.

Treatment Put on Bradford frame and given 6 arsphenamin injections and 25 inunctions.

Response Immediate Finger and toe healed. Marked improvement in back.

Cardiovascular Examination (Willius):

Short of breath since influenza.

Heart 4 by 8 cm. N arhythmia. Systolic murmur at base, maximum at aortic area.

Increased aortic dulness.

Electrocardiogram: Rate 128 shows tachycardia.

DISCUSSION

1 Aortitis and aneurysm in children with heredosyphilis are genuine rarities in my experience. This may have been an infection acquired t birth.

2. Did the boy actually have syphilis? Without the aortitis and aneurysm the findings in the case would be thin, for the remainder of the picture including the weak positive Wassermann reaction might have been that of tuberculosis.

3. The therapeutic response was little too good for tuberculosis alone, although arsphenamin can produce marked improvement in tuberculosis.

4 The entire picture except perhaps the von Pirquet, might conceivably have been the work of syphilis, even to erosion of the vertebral bodies by aneurysm and deformity and pain simulating Pott disease. It is also easily possible that the process in the spine as syphilitic gummatous osteitis.

5. In such complexes it may be impossibl to disentangle the two diseases, but they need not interfere with treatment for syphilis. In such case it ould be inexcusable not to employ it, even had there been no aneurysm.

if the symptoms suggest aneurysm, one cord may be paralyzed without hoarseness (New). The response of pain and dyspnea, and not infrequently of hoarseness, to treatment must be the guide to improvement and is often quite convincing.

Aneurysmal Erosions.—Erosion by aneurysmal pressure may be confused with tuberculous and carcinomatous metastatic lesions of the spine (Fig 697). In aneurysms of the descending aorta from the median thorax down, and in

high abdominal aortic aneurysms, it is particularly important to keep in mind the possibility of confusion with Pott s disease which the radicular pains may suggest. In fact, in interpreting aneurysmal symptoms both within and without the thorax, it is always important to keep in mind their referred character and to recall that the pain of an aneurysm of the descending aorta may be felt in the epigastrium, while the physical signs may be found only on examination of the back. The symptoms of abdominal aneurysm may lead to surgical intervention for a supposed pancreatic lesion. Here again if the serologic test gives the clue, the response to treatment for syphilis may make the diagnosis, and afford relief.

The diagnosis of the unusual types of aneurysm is illustrated in the case sketches, and is a combination of knowledge of the anatomic position of the vessel, the pressure symptoms to which its enlargement may give rise, the identification of *expansile pulsation and bruit*, and the *signs of disturbed* arterial rather than venous circulation.

The Signs of Mediastinitis.—These, when they appear as accompaniments of thoracic aneurysm, are identical with those described for syphilitic mediastinitis in general on page 1173

The Signs and Symptoms of Coronary Sclerosis.—Angina pectoris and the general symptomatology of coronary sclerosis play a particularly important rôle in treatment decisions involving syphilitic aortitis. For this reason the symptomatology of angina pectoris is reviewed in parallel column with that of coronary thrombosis in Fig. 698, even though the rôle of syphilis in the production of coronary thrombosis particularly is not generally accepted by clinicians as especially important. It must be said, on the other hand, that this question is far from evaluated. Certainly it cannot be answered, as will presently be seen, by limiting the definition of syphilis to those patients who have positive blood serologic reactions, as in Levine s monograph. Particularly should the nervous system be carefully investigated for supportive evidence. When all is said and done, however our own experience is in accord with the literature to the effect that if a distinction is drawn between paroxysmal pain other than the distinctive Heberden anginal attack, coronary disease is, relatively speaking, the least important of the four groups of symptoms—aortitic, aneurysmal, myocardial and coronary which one encounters in clinical cardiovascular syphilis.

Even though this be true the seriousness of coronary symptoms in the course of syphilitic cardiovascular disease cannot be exaggerated. Willius and Brown found syphilis in 19 per cent of 86 patients coming to necropsy with coronary sclerosis. The history of anginal attacks or of a tendency on the part of the precordial pain of aortitis to radiate into the arm shoulder or neck, is a warning of the utmost gravity indicative of threatened injury to the blood supply of the heart, whether from the course of the disease or as a result of coronary atresia from misdirected and overstrenuous treatment of aortitis. Any increase in the severity of the pain seizure, in its frequency in the diminished exercise tolerance of the patient, is a warning of an unpropitious course. Transient difficulty however may be overcome under the continuance of treatment—but it is decidedly more probable in our experience, that the outcome will be disconcerting. An invaluable guide to the extent that the myocardium has been damaged by the coronary lesion and the degree of overload it can sustain during treatment is obtainable in advance from the electrocardiogram

The recognition of anginal symptoms in any patient should, of course, be the signal for the application to his case of all the test criteria enumerated in the discussion of early aortitis, and particularly to the roentgenological study of the aorta. In patients exhibiting atypical aortic pain marked nervous reaction during the attacks or outright evidence of psychasthenia and hysteria, the possible instrumentality of syphilis should by no means be waived and the case should be investigated to the bottom. We, even in a limited experience, have had occasion to reproach ourselves more often than otherwise for over

Fig 498.

SYMPTOMATOLOGY OF ANGINA PECTORIS AND CORONARY THROMBOSIS

Angina Pectoris	Coronary Thrombosis
1 Pain in the chest, radiating into arms, usually left; into shoulder neck, epigastrium.	1 Pain in the chest, viselike, griping or squeezing with the usual radiation.
2. Patient remains motionless, pale.	2. Patient shows agitation and shock, often restless and thrashing around, or may collapse, fall, lose consciousness.
3. Pain of short duration, paroxysmal. Increasing frequency of attacks common	3. Pain of prolonged duration, hours or days, though may have been preceded by paroxysms of angina.
4. Pain usually brought on by exertion, anger exposure to cold.	4. Onset frequently when at rest, at meal, or in sleep.
5 Vomiting less common.	5. Vomiting common ("acute indigestion").
6. Pulse little change	6. Pulse small, weak, rapid, but these changes may be delayed several hours.
7 Blood pressure often elevated or unchanged, but may be low	7 Blood pressure falls.
8 No pulmonary symptoms or dyspnea, no râles.	8. Pulmonary edema may occur. Râles usually present and dyspnea.
9 Liver no change	9 Liver tender and enlarged.
10 Abdomen usually soft.	10 Abdomen often rigid.
11 Heart sounds usually normal, no arrhythmia.	11. Heart sounds, especially the first, very weak and distant, the latter often absent, sometimes gallop rhythm.
12. Fever and leukocytosis absent.	12. Fever and leukocytosis frequent after several hours.
13. Nitrite or nitroglycerin relief	13 No nitrite relief
14 No pericardial rub.	14 Pericardial friction rub may be heard.
15 Death rare in first attack of true angina.	15. Attack prolonged over days with evidence of cardiac failure.
	16 Embolic accidents from mural thrombosis.
	17 In abdominal cases there may be signs of an acute surgical abdomen and even jaundice.

emphasizing the functional Women and physicians are too apt to have their cases lightly estimated

Cardiologists of great experience hesitate to make a sharp differentiation between true angina pectoris and those neuroses which may very closely simulate it When a cardiologist makes the latter diagnosis he usually crosses his

Wolferth et al. (personal communication) state that the characteristics of pain in angina pectoris and coronary thrombosis are about the same so far as location, distribution and type of pain are concerned The pain tends to be more severe and is greatly prolonged in coronary thrombosis. The abdomen is not actually rigid in coronary thrombosis, but distention is frequently present. The liver does not become tender until after enlargement has occurred which is exceptional in the acute stage

fingers and often waits only to see the patient develop true attacks of angina a year later or worse still, to see the poor "neurotic" die during an attack of real angina. In a goodly percentage of cases, however there are a few criteria which often help one to differentiate between the two conditions and these are given in *Fig 690*

The electrocardiographic identification of disease of the coronary arteries is growing in importance especially since Wolferth and Wood's work on the precordial leads. At the close of an excellent symposium on coronary disease (Proceedings of the Staff Meetings of the Mayo Clinic, 17 305 1944) however Barnes, after pointing out variety of abnormalities and particularly the value of the EKG in myocardial infarction, felt obliged to say that too much reliance is placed on the electrocardiogram in the identification and exclusion of disease of the coronary arteries.

Fig. 690

DIFFERENTIATION OF "TRUE" FROM "PSEUDO" ANGINA

Heberden's Angina Pectoris	"Neurotic" Angina Pectoris
1 Pain usually definitely related to exertion. (After meals—cold blustery days—physical exertion.)	1 Pain variable. (Most often emotional exertion.)
2. Location—substernal.	2. Location—most often precordial.
3. Character Deep pressure—crushing, viselike constriction. Heavy feeling—weight. Burning.	3. Character Knifelike. Sharp.
4. Pain stops the patient on the spot—walking—leaning against all—lying down—sitting up.	4. Patient runs around—causes great commotion.
5. Radiation—varies considerably Arms, chin, neck, epigastrium—gallbladder region. Appendix, thigh.	5. Radiation. Much the same.
6. Relief By stopping. By nitrites—inconstant.	6. Relief Moving about. Drugs less effective.
7 Sense of impending death questionable.	7 Sense of impending death may or may not be present.
8. Facies Awestruck; ashen sweat on forehead; quiet.	8. Flushed—Patient voluble.
9. Dyspnea absent. Quiet breathing.	9 Breathes heavily
10. Blood pressure usually rises 10 to 20 mm. May stay at normal.	10. Rises.

Sprague (1942) from Massachusetts General Hospital material pointed out the frequent association of high degrees of coronary obstruction, with bundle branch block.

The attack of abdominal angina, as described in Fig. 700 may as Willard Stone points out, be confused with reflex disturbances from chronic cholecystitis. The short duration of the typical anginal seizure differentiates this satisfactorily from the confusion elements enumerated by Levine in the abdominal symptomatology of coronary thrombosis. Stone also mentions myocardial fatigue-states in overactive patients with marked arterial hypertension as being capable of producing chest pains distinguished with *difficulty from* angina pectoris and disappearing on proper rest.

Wolferth *et al.* (personal communication) state that anginal pain is usually relieved by nitrites; in fact, failure to obtain relief brings the diagnosis into sharp question.

Anginoid pain not infrequently has to be differentiated from syphilitic angina. Among the more important causes of anginoid pain are substernal pain due to hiatus (diaphragmatic) esophageal hernia (Jones, 1941), profound anemia (Bernstein and Ginsburg, 1941), myxedema (Perl, 1943), herpes zoster (Gale and Abrahamson, 1939; Spillane and White, 1939; Parsonnet and Bernstein, 1939) cervical rib (Reid, 1939), hypertrophic spondylitis (Willius, 1938) osteoarthritis of cervical spine (Nachlas, 1934) a manifestation of male climacterium (McGavack, 1943), mediastinal tumor (Pardee, 1933, Fenn, 1936), deformities of the thoracic spine (Smith and Kountz, 1942) and cellulitis of the breast (Nell, 1932) Semmes and Murphey (1943) in particular

[illegible]

Fig 700 —Reproduction of the recorded history of patient with abdominal angina pectoris.

DISCUSSION

1 The patient specially remarked on the fact that his epigastric pain followed exertion with the arms, such as pushing a door or turning the steering wheel of an automobile

2 On examination an aortic roughening was detected, the blood Wassermann reaction was strongly positive the x-ray of the chest showed no abnormality The right lobe of the liver was enlarged and the edge tender There was an inequality in blood-pressure between the two arms that suggests an unrecognized aneurysm, though no trace of one could be found Blood-pressure right 120/50, left 90/60. There were neurologic signs suggestive of neurosyphilis, but no spinal fluid examination was performed on account of the patient's departure The electrocardiogram showed T-wave negativity in Lead I of grave prognostic significance.

3 The stomach was negative to x-ray and test-meal.

There is often resemblance in the history to that of aneurysm of the arch. Abdominal angina pectoris should always be carefully studied for signs of aneurysm.

have reported two physicians and a woman in whom rupture of the 6th cervical intervertebral disk very closely simulated repeated coronary seizures.

As a final point of emphasis Fig 701 may be used to bear home the lesson that advanced coronary sclerosis does not necessarily carry with it the warning signs of anginal seizures. We were impressed several times in our unfavorable outcomes with the very great difficulty of estimating from the clinical side the degree of actual coronary injury in patients whose markedly unfavorable re-

Fig. 701.

CARDIOVASCULAR SYPHILIS AND NEUROSYPHILIS. DEATH UNDER TREATMENT. ADVANCED CORONARY SCLEROSIS OF A GRADE NOT SUSPECTED DURING LIFE

A woman, aged thirty-five years, married, housewife.

Examined 11/22/1920.
No History of Primary or Secondary Syphilis.
One Miscarriage
Duration of Symptoms Ten years.
Onset gradual, with vomiting during the first two years.
Symptoms
Precordial pain, steady moderate, non-radiating.
Fatigue.
Dyspnea, two years duration.
Cough, nocturnal, choking
Palpitation, tachycardia, five years.
No *definite anginal attacks.*
No *edema or anasarca.*
Physical Signs
Heart greatly enlarged.
Auricular fibrillation.
Ventricular extrasystole
Murmurs, systolic, diastolic.
Thrill, aortic area.
Pistol shot, Corrigan and capillary pulse.
Blood-pressure Systolic, 140 *Diastolic not obtainable*
Urine normal.

Spinal Fluid, Wassermann reaction positive Nonne reaction negative, 48 lymphocytes.
Neurologic Signs: Pupils irregular unequal, but reacting well. Few sensory but no important reflex changes.
Treatment: Rest in bed with mercurial preparation for arsphenamin.
Mercurial preparation Ten injections mercury succinimid (1 gr daily) intramuscularly
Arsphenamin Injections 0.2 gm 0 4 gm., 0.3 gm., 0 3 gm., intravenously at weekly intervals, begun after tenth injection succinimid.
Succinimid continued to 20 injections.
Improvement Marked: Dyspnea, pain, and fibrillation disappeared, heart reduced in size.
Patient Died Suddenly in Bed six hours after fourth arsphenamin injection.
Necropsy: Far advanced aortic valvulitis; valves reduced to stubs. *Total obliteration left coronary artery* Only fibrous cord with few necrolations could be found.

DISCUSSION

1. **In advanced grades of valvular involvement the involvement of the coronaries may be expected to be severe The symptoms may not be a guide. Even in mild grades of aortitis coronary changes may be so severe as to menace life.**

2. Coronary involvement may be severe without definite anginal attacks.

3. **A careful estimation of life expectancy is a valuable element in deciding the treat**ment applicable to a given case.

4 **The combination of cardiac and neurosyphilis is not rar**

5 The risk is always great, the cardiac condition, because it limits treatment, being the more serious element. Prognosis is, to some extent, proportioned to the severity of the heart lesion. The cardiac symptoms may completely dominate the case and overshadow the neurologic symptoms.

6. **This patient was a wreck.** Cardiac dilatation, fibrillating auricles, and low diastolic pressure are warnings of the hopelessness of the case, the extent of structural damage, and the impossibility of attaining radical results.

7 **This patient was overtreated.** Mixed treatment by mouth with rest in bed for weeks might have prolonged life probably it could not have affected the neurosyphilis.

8. **Arsphenamin, because it administers a therapeutic shock (Herxheimer reaction) because of the rapidity of the healing changes it produces, and because of its vasculotoxicity is dangerous to bad hearts.**

9 **The arsphenamin dosage was too large for such a case, and neo-arsphenamin was** probably to be preferred. The first dose should not exceed 0.03 gm the last, 0 6 gm.

10. **The treatment of the neurosyphilis should have been secondary If the car**diac condition ever improved enough to warrant it, intraspinal measures should have been used.

11 **Intraspinal treatment after a long mercurial preparation or tryparsamide is the method of election in combined neurosyphilis and cardiac syphilis.**

sponse to treatment and in some cases necropsy findings proved the presence of what should be regarded as an absolutely contraindicating degree of involvement from the standpoint of intensive treatment.

Myocardial Symptomatology.—The occurrence of sudden death from an acute exacerbation of syphilitic latent myocarditis has already been discussed. The recognition of myocardial involvement in the later years of the disease, unfortunately is none too satisfactory The electrocardiograph must in all probability furnish the chief reliance. There are no specific symptoms of syphilitic myocarditis, electrocardiographic or otherwise. Shortness of breath on small provocation diminishing exercise tolerance, weakness either in the circulatory readjustments of the early morning or in a gradual shortening of the period of effectiveness during the day· slight edema of the extremities signs of dilatation weak action and distant sounds, low blood pressure, persistent well-defined tachycardia or bradycardia and the arrhythmias indicative of organic disturbance such as conduction block, are the familiar signs. The rarity of auricular fibrillation in the syphilitic heart, as contrasted with its frequency in rheumatic fever has been mentioned by Carter and Baker as a significant differential point.

SPECIAL DIAGNOSTIC PROBLEMS

The Collateral Evidence of Syphilis.—Diagnostic or confirmatory evidence of the presence of syphilis, apart from the serological tests, is even yet not sufficiently searched for in the presence of cardiovascular disease and even of aortic regurgitation itself In illuminating this aspect of the diagnostic problem, Stokes's Mayo Clinic material of 190 patients with cardiovascular syphilis was particularly serviceable. No history pointing to a syphilitic infection could be obtained in one third of the cases. A surprisingly large proportion of those in whom a venereal history was taken had had gonorrhea (81 per cent) *as compared with 60 per cent in most of the surveys*. Nearly 20 per cent could give no history of a primary lesion or other syphilitic manifestations but had had gonorrhea.

Chief reliance in diagnosis must rest upon two groups of findings the serological test and the examination of the nervous system, including that of the spinal fluid To these might well be added the therapeutic test, for reasons presently enumerated.

The Serological Tests in Cardiovascular Syphilis.—Moore, Danglade and Reisinger have reported 75.5 per cent positives in their series of cases of syphilitic aortitis. Carter and Baker reported 92.6 per cent in their first hundred cases. Miller (T H) on our service at the University of Pennsylvania, obtained 81.8 per cent positive Kahn reactions in cardiovascular syphilis, and 84.8 per cent positive Kline reactions (slide precipitation test) McIntyre and Gilman found the Kahn test to be more sensitive than the Kolmer Wassermann in cardiovascular syphilis (96 tests in 25 cases). In the literature prior to 1916, Elliott placed the margin of error of the negative blood Wassermann reaction in syphilitic vascular disease as high as 40 per cent. In 31 necropsies in cases of syphilitic disease of the aorta, Reid reports that 17 per cent were Wassermann-negative on the blood shortly before death. In Reid' American Heart Association symposium series, positive Wassermanns were obtained in 78 per cent of cases. Cannaer and Dexter obtained 73 per cent positives in 80 cases and Longcope 74.5 per cent positive in 47 cases. Levine found 30 per cent negative in 40 cases (American Heart Association symposium) and Willius in 100 selected cases of syphilitic cardiovascular disease found 65 per cent Wassermann positive in aortitis, 82 per cent in aortic insufficiency and 85 per cent positive in aneurysm. Longcope observed the same higher proportion of positives in aneurysm as compared with aortitis. Other figures including CCG (1930), White and Wise (1937) Arkin (1934) Wile and Snow (1939), Kampmeier (1938)

Levitt and Levy (1940), Nichols (1940) Willius (1941), McDermott, Tompsett, Webster (1942), Levitt and Ireland (1942) have yielded essentially similar data. Beckh (1943) has collected the recent literature bearing on the serologic reaction in cardiovascular syphilis. In study of 100 cases of cardiovascular syphilis, *diagnosed at autopsy*, in which the serologic reactions had been done by modern technic, he found of 49 cases of aortic insufficiency or aneurysm or both, in 43, or 88 per cent, there was positive Wassermann or Kahn or both on first examination. *Of 51* patients with uncomplicated aortitis, 80 per cent had positive serologic reaction. In none of the cases of aortitis was the diagnosis made clinically

Of the 49 patients with clinically diagnosable cardiovascular syphilis, i.e., aortic insufficiency or aneurysm or both, 96 per cent had either positive Wassermann or Kahn or both, or history of positive Wassermann in the past, or lastly history of previous antisyphilitic treatment.

The proportion of serologic negativity in the neurological phases of vascular disease of the nervous system is fairly high. The proportion of serologic negativity would be higher in the field of cardio-aortic disease were clinicians more alert to the possibility of negative bloods and willing to subject patients



Fig. 702.—Arciform, crescentic late nodular syphilid of the forearm. The patient and her examiner thought she had eczema. She had the aortitis described in Fig. 703.

with contestable negative serologic reactions to therapeutic tests. Of this our material gave a number of excellent examples (Figs. 702, 703)

False Positive Serologic Reactions in Cardiovascular Disease.—Any survey of an invisible aspect of syphilis is affected by the fact that it takes courage to attach the clinical diagnosis to patient with negative serologic reaction. This fact probably influences all returns on the *proportion of positive and negative blood serologic reactions in cardiovascular disease* and all clinical observations on the influence of syphilis in their production. One of the most instructive features of the case abstract is the proof they offer that the blood serologic reaction may present all grades of fluctuation, from complete and persistent negativity to complete and fixed positivism, in patients with all grades of involvement of the vascular system.

The finding of positive blood serologic reaction is most often open to question in connection with aortic valvular disease accompanying mitral lesions. Stokes has seen at least eight examples in which repeated strongly positive blood serologic reactions were obtained with endocarditic manifestations, obviously of septicemic or subacute bacterial type This is certainly *small but by no means negligible* proportion. *In several of these cases* clinical examination (Fig. 704) made the probability of syphilis extremely slight, and even at necropsy convincing evidence of syphilis was hard to find. In febrile cases, therefore, certain amount of confusion is inevitable On the other hand, so far as the acute rheumatic fever problem is concerned, w have seen no satisfactory evidence of definite tendency to false positiveness in serological tests.

Fig. 703.

CUTANEOUS SIGNS OF SYPHILIS IN THE IDENTIFICATION OF EARLY VASCULAR LESIONS. THE PRESENTING SIGNS OF EARLY AORTITIS

A farmer's wife, aged forty-two, examined 1916.

Chief Complaint Pressure in the chest. "Eczema" left forearm, desired general examination.

Her First Examiner Noted the Following:
Complaint of throbbing at the back of the neck.
Tightness in chest at times amounting to pain on exertion.
Slight headache slight *dyspnea*, cold numb arms.
Filled teeth, epigastric tenderness.
"*Many reddened areas* on left forearm.
Blood-pressure 146/78.

Heart Described as Negative: Noted, however that second sound was somewhat accentuated.

Blood Wassermann Negative.

Dermatosyphilologic Examination: Patient would not undress, saying she came only for eczema on the arm.

The Lesion on the Forearm is Indurated Arciform, and Leaves a Slight Atrophic Scar

The patient denied infection with syphilis or gonorrhea

"**The Cutaneous Lesion is None the less Almost Certainly Syphilid** in spite of the negative blood Wassermann."

Provocative Procedure Negative throughout.

The Lesion, However Vanished Within Eight Days.

On reconsideration and discussion, the patient admitted exposure at age eighteen

Internist Asked to Reconsider General Findings Consultant (Wilhus) reports *Heart not enlarged.*

Accentuated second sound, especially at aortic area.

Low reverberant systolic murmur at aortic area, not transmitted.

"**This, with the History of Retrosternal Pain, Make Aortitis Quite Definite**

Pupils reported very sluggish to light.

This Patient was Placed on Vigorous Treatment with Arsphenamin and Mercury and repeatedly studied during the next four years to watch the progress of the aortic lesion.

She Has Never Had a Positive Blood Wassermann Reaction, and the spinal fluid is normal.

The Valvular Lesion Passed Through a Stage of Accentuation (therapeutic paradox) in which the murmur became audible in the carotids, then much louder always with accented second sound.

Diastolic Murmur was First Recognized Fourteen Months After Her First Examination Pain in chest became more marked. For a short time the systolic murmur disappeared. Blood-pressure ranged from 146/80 to 160/86. Transient slight edema disappeared with tincture digitalis 10 minims t. i. d.

Then the Findings Became Stationary and have remained so for four years, with the patient in excellent health.

x Ray showed only slight enlargement. Electrocardiograms repeatedly normal

This is the Stage at Which Syphilitic Aortitis Should Be Recognized for satisfactory therapeutic results.

DISCUSSION

1 The cutaneous lesion in appearance and behavior under arsphenamin was, beyond reasonable doubt, a syphilid. Note how completely it was underestimated by the first medical examiner

2 Note that dyspnea, precordial distress, slight hypertension, and accentuation of the aortic second sound were all significant points overlooked by the examiner when it came to interpretation, though he observed most of them.

3 The definite recognition of the early systolic murmur may have been the result of the action of treatment on the aorta or valve between first and second examinations, or have been identified by more expert auscultation.

4 The later appearance of the diastolic murmur marks the development of insufficiency probably from shrinkage of the cusps in healing, for there was no subsequent evidence of an advancing process instead of a healing one

5 As the insufficiency developed transient signs of a strain on compensation appeared, but were relieved by digitalis.

6 There is no evidence to date of an advance of the process either at the valve or in the myocardium as in some of the late cases here described

7 The blood Wassermann reaction has played no part in the diagnosis. Serologic negativity in vascular syphilis is not rare In late syphilis clinical signs here take complete precedence over laboratory syphilology when they are present It needs only that the physician shall recognize and correctly interpret them.

A modern serological test may then be relied upon in suspected untreated vascular syphilis to identify the presence of the infection in from 70 to 85 per cent of cases

The Provocative Procedure.—We no longer employ this procedure when cardiovascular syphilis is suspected.

The "No History of Syphilis" and Blood Sero-negative Group.—Thoroughgoing inquiry into the history of syphilis is sometimes neglected in cardiovascular cases. In 30 of the series of 190 patients, no serious attempt had been made to elicit a history of syphilis or at least to record one.

Fig. 704.

THE BIOLOGIC FALSE POSITIVE BLOOD WASSERMANN IN SUBACUTE BACTERIAL ENDOCARDITIS

Female, aged eighteen, single.

Chief Complaint: Pain in legs and palpitation. Palpitation three years, pains five months.

Pains in Back and Legs Followed Trouble with Wisdom Tooth and Fever.

Painful Nodes Developed on both feet. Evening temperature 100 101 F Weight loss 35 pounds.

Urine Negative. Hemoglobin 85 per cent. dropped 10 per cent. in ten days.

Leukocytes 8000 to 12,400.

Physical Findings Double murmur over hole precordium. Water-hammer pulse. Femoral pistol shot. Heart enlarged to left (x-ray) Electrocardiogram, inverted T all leads.

Blood-culture Streptococcus viridans.

Blood Wassermann Reaction Strong positive.

Dermatosyphilologic Examination
Multiple petechiae.
No adenopathy
No abnormalities of any structure diagnostic or suggestive of syphilis.
Intact virgin.

Blood Wassermann Strong Positive on repetition.

Death from endocarditis and bronchopneumonia. Autopsy refused.

Diagnosis Double aortic lesion, poly valvular insufficiency subacute bacterial endocarditis, streptococcus septicemia.

Discussion

There seems no reasonable doubt, even without autopsy that this young girl did not have syphilis. The aortic lesion was apparently streptococcal, and the repeated positive blood Wassermann, as in other cases have seen, biologic f lse positive.

Of 56 patients, all presenting physical evidence of cardiovascular disease but seronegative at the outset, 12 proved after the most critical examination to have what amounted to "no case for cardiovascular syphilis. This constituted margin of 20 per cent error in seronegative cases. Of the 47 patients having no recorded history of syphilis, 43 per cent gave history of gonorrhea, 60 per cent were Wassermann-positive, 36 per cent had positive neurological signs, 30 per cent positive spinal fluids, and 24.5 per cent positive roentgen-ray signs. Of the Wassermann-negative group of 56 patients, 67 per cent had positive history of syphilis, 44 per cent positive neurological signs, 32 per cent positive spinal fluids, and 80 per cent positive roentgenographic signs.

Syphilis of the Central Nervous System in Association with Cardiovascular Disease—From this group of manifestations great assistance in diagnosis may often be had. Neurosyphilis was present in 54 per cent of the Mayo Clinic series. The value of the routine spinal fluid examination is apparent from an incidence of abnormal spinal fluids in 40 per cent, though as Reid wisely remarks, the mere presence of coincident neurosyphilis does not prove the

vascular lesion to be syphilitic. The neurological examination reveals neurosyphilis more frequently than the spinal fluid (49 per cent) which is to be expected from the well-recognized occurrence of complete serological negativity in vascular neurosyphilis. Asymptomatic neurosyphilis appeared in only 5 per cent of our series, a situation to be expected because of the long duration of the disease in this group The routine spinal fluid examination and the neurological examination must therefore be regarded as integral parts of the study of every syphilitic patient suspected of having cardiovascular disease and as part of the examination of all suspected cases, unless positively contraindicated by age or grave illness. High-grade meningeal and parenchymatous changes may be associated with vascular syphilis, and the clinical picture may range from hemiplegia with complete serological negativity to paresis with strong and irreducible positive Wassermann reactions and pleocytosis in the spinal fluid In fact, the frequency of cardiovascular syphilis in paresis and tabes has been a matter of general recognition for a number of years.

The figures in the literature show wide variation, depending on the thoroughness of the investigation for neurosyphilis and on necropsy control. A excellent review of these figures is given by Herxheimer (Jadassohn Handbuch) From 15 to 20 per cent of paretics clinically present aortic disease, the estimates based on necropsy however ranging from 62.5 per cent (Glasberg) to 87 per cent (Coppola) In tabes the clinical frequency of aortitis ranges from 11 per cent (Nonne) and 26 per cent (Musser and Bennett) to such high proportions as Kessler's 60 per cent. Musser and Bennett found that in 102 cases of vascular neurosyphilis, 88 per cent had late syphilitic aortitis, and 8.9 per cent had advanced to the stage of aneurysm. In 110 general paralytic cases, 28 per cent had syphilitic aortitis with 3 4 per cent aneurysms and 26 per cent of 20 tabetic necropsies revealed syphilitic aortitis with no aneurysm. Advanced syphilis of the aorta and resulting aneurysms were more frequent in association with the endarteritic and meningeal forms of cerebrospinal syphilis than w th the parenchymatous (tabetic and general paralytic) types. The obverse of the picture, which is more important for the diagnosis of cardiovascular syphilis, is represented by range of 16 to 33 per cent for the incidence of tabes in patients with aortitis. Hubert s finding of 23 per cent tabes in 220 patients with aortic syphilis (1919) is fairly typical. In general, the frequency of combined cardiovascular and neurosyphilis increases with advancing years.

More recent figures including CCG (1936), Wile and Snow (1938) Levitt and Levy (1940), Stroud (1945) continue to show wide variability in incidence of neurosyphilis in association with cardiovascular syphilis. In interpreting any of these figures one must remember that investigation for neurosyphilis is usually done only on suspicion and often omitted in cardiac wrecks. Therefore the actual incidence is probably greater than that reported

A number of authors have called attention to the relatively benign course of aortic syphilis coincident with neurosyphilis in the same individual Schlesinger and Wagner-Jauregg have found cardiac deaths among paralytics, for example, to be a rarity It is suggested, too, that the neurosyphilis in patients with marked syphilitic cardiovascular disease tends to run an abortive course. The rarity of aneurysm in tabetics and paretics is emphasized by Herxheimer

The more recent statistics by Willius rendered in tabular form in Fig. 45 are both a summary and a guide to the frequency of collateral evidence of syphilis in a typical thoroughly examined and well digested material on cardiovascular syphilis.

The Therapeutic Test in Early Aortic Syphilis.—The worth of this resort in diagnosis has, we believe received insufficient attention from clinicians. If the tambour second sound and the aortic systolic murmur are the earliest evidence of change in the aortic wall and its surroundings, the identification of these signs in young persons without hypertension or with suspicion arousing fluoroscopic signs in whom even a moderate degree of suspicion of

syphilis may be raised calls, we believe, for consideration of the therapeutic test. This is especially true in patients placed under modern treatment for early syphilis and carried through observation with long periods of seronegativity punctuated occasionally let us say by slight positives, or in patients returning to observation after prolonged lapse. The therapeutic test also has important applications in seropositive latent syphilis in younger persons in whom the first suspicion-arousing signs of aortic disease may appear

McDermott, Tempsett and Webster (1946) though using methods for detecting cardiovascular abnormality (vital capacity venous pressure and circulation time) in addition to roentgenoscopy which are not available to the average clinic, clearly showed the relatively long duration of the now commonly accepted asymptomatic period in syphilitic cardiovascular disease. The finding of presumptive evidence justified treatment for syphilis to prevent further involvement. In only 2.2 per cent of their patients were the serologic tests negative in the absence of history of previous antisyphilitic treatment.

Fig. 705.

100 CASES OF CARDIOVASCULAR SYPHILIS REPORTED BY WILLIUS, 1930
(The figures represent per cent positive to the nearest integer.)

Symptom or sign.	Aortitis, 17 cases.	Aortic regurgitation, 59 cases.	Aneurysm, 24 cases.
Blood Wassermann reaction	65	[illegible]	[illegible]
Abnormal spinal fluid	18	20	25
Other forms of syphilis present	24	29	21
Painful seizures	18	25	48
Significant electrocardiographic abnormalities	71	65	17

In the interpretation of such a therapeutic test it is important to understand the mechanisms involved. In very early aortic syphilis up to and including the period of early valvular sclerosis, it is entirely safe to employ a therapeutic test, unless there is definite evidence of coronary disease. A number of excellent examples of its usefulness will be found in the clinical cases. The course of a therapeutic test may follow either of two directions, as far as signs and symptoms go, depending probably on the duration of the process and the extent of permanent replacement of healthy by inflammatory or scar tissue. From our observations it is difficult to predict clinically that the valve is undamaged, even though only a tambour second sound may be identified. When the patient is placed on treatment, a succession of changes may occur which carries him through the sclerosis and increased rigidity and may form the basis of a systolic murmur and tonal changes to the diastolic murmur that marks the sclerotic distortion of the healed or healing, probably fibrous, valve flap Clinically speaking, one might conceive that such a patient, as a result of his therapeutic test, is in a last state which is worse than his first, in that for a competent valve an incompetent one has been substituted. In a sense this patient has undergone a therapeutic paradox in the process of attaining a diagnosis. On the other hand, the institution of treatment may

cause a prompt and marked remission or complete disappearance of all clinical symptoms and signs.

The Paradoxical Increase in Signs.—The paradoxical increase in signs on the institution of treatment in early aortitis, whether with diagnosis or for therapeutic test, was observed not only in the Mayo Clinic material but subsequently at the University of Pennsylvania and has had confirmation by Moore Danglade and Reisinger Observation of such patients for a period of several years, as in certain of our cases, corrects the impression above mentioned that the last state of the patient is worse than the first. It indicates clearly that the patient has in reality exchanged a progressive disability for an arrested and static one (Fig. 703) He can now proceed to compensate for a slight regurgitation in a healed lesion, instead of finding himself some years later the possessor of a broken compensation resulting from a progressive lesion, and finally an irremediably ruined aortic valve.

For example, a patient may not present a murmur at the outset, merely an accentuation of the aortic second sound. Two or three months or even three or four weeks after treatment is begun a soft blowing, systolic aortic murmur may be recognized and may grow to a rough systolic murmur and become stationary while the patient exhibits, coincidently a slight rise in blood pressure and slight but transient myocardial embarrassment. The precordial pain may on the other hand, vanish coincidently with the first stage of treatment, the dyspnea may disappear entirely or if the myocardial effect is marked may increase and then subside. Transient edema may appear In very early angina pectoris the symptoms may show improvement from the start, but if the coronary lesion is of long standing and myocardial damage is definite, there may be a very pronounced and even injurious exacerbation. For this reason it may be well to carry out therapeutic tests, even on early lesions, with the patient at rest, although in a way the alteration of the mode of life makes the subjective part of the test less clear cut. The circumstances must be adjusted to the individual case and to the information which is sought. If the systolic murmur was marked at the outset, the later appearance of diastolic murmur under treatment may be expected, probably as the physiologic expression of contraction of the healing valve flaps. In such cases compensatory myocardial hypertrophy will probably be more marked, and myocardial stress temporarily more pronounced.

The prolonged watching of the progress of a therapeutic test is obviously of the utmost importance, although the examiner should not expect rapid and immediate changes. The lapse of from six weeks to three months before the changes associated with healing become easily detectable by physical signs is not at all unusual. The symptomatic responses, while usually more rapid, may be similarly delayed The serologic tests should be repeated at the outset if the first blood serologic reaction is negative and occasional single repetitions may after a time show an undoubted swing toward the positive. The technic of the therapeutic test is discussed under treatment. The use of the therapeutic test in differentiating aneurysm from mediastinal tumor is considered on page 937 in connection with roentgenological diagnosis.

The Rheumatic Fever Question.—We have already reviewed the symptomatic and objective differentiation of syphilitic and rheumatic aortic valvular disease (see p 907)

Coincident involvement of the mitral valve points toward the septic or rheumatic origin of an aortic lesion, although, as Hirschfelder points out, systolic murmur t the apex in a syphilitic aortic lesion, due to relative mitral insufficiency is not uncommon. Warthin says that he has never found syphilitic lesion of the mitral valve.

The influence of streptococcal and rheumatic infection on the aortic valves, without a mitral complication, is as yet hardly evaluated clinically for means of detecting syphilis in the seemingly rheumatic patient are still only em-

ployed in the most rudimentary way by the majority of physicians. A negative history of syphilis and a single negative blood serologic reaction with a history of tonsillitis, pains in the joints or acute rheumatic fever in a young adult, are still accepted by many physicians as eliminating syphilis from the possible explanations of aortic systolic murmur While this uncritical attitude persists, it will often be impossible to recognize syphilis of the aorta in the first decade of the disease, when its diagnosis means the most in outlook for the patient. The more uncritically the term "rheumatism" is used the larger will be the proportion of patients to escape through this loophole and develop the late complications of cardiovascular syphilis. We have pointed out in previous chapters how well an early syphilitic infection with arthritic manifestations in which ostealgias, myalgias, hydrarthroses, and so forth are indiscriminately jumbled, can imitate "rheumatism" clinically Even to the examining eye deception is sometimes easily possible, to say nothing of the untrustworthiness of the patient's history Due allowance must, of course, be made for the clearcut picture of acute rheumatic fever which should be sharply differentiated in its historical and diagnostic value from the muddle of "rheumatism" arising from catch-basket use of the term.

Rheumatic aortitis has been discussed by Osler and cases have been reported by Klotz, Renon, Baris, P whski, and others. Bennert formulated, on the basis of 20 cases, rule which certainly deserves critical reexamination in the light of modern syphilology that aneurysm in children and in youths is result of rheumatic fever A tendency to spontaneous recovery in such cases is marked. Mamorstan and Kraus have described influenzal aortitis, Allbutt speaks of aortitis as complication of suppurative infections, erysipelas, smallpox, typhoid fever diphtheria, measles, scarlet fever pneumonia, tuberculosis, and gonorrhea, but fortunately other observers also with extended experience, such as Elliott and Reed, concede it to be very rare.

"Rheumatism" in the Mayo Clinic Case Study —In an examination of the complaint of rheumatism in the present cross-section, it was found to resolve itself into almost everything imaginable, from true multiple arthritis following scarlet fever and repeated attacks of tonsillitis, to the pain of slowly developing subclavian aneurysm without aortic signs, and the neuritic pains of early tabes dorsalis. The physician who asks his patient if he has had rheumatism and tonsillitis, or who obtains what he believes to be history of acute rheumatic fever and then proceeds to remove tonsils for the treatment of aortic endocarditis after obtaining single negative blood Wassermann reaction, may be overlooking good story of syphilis in disguise and missing syphilitic aortitis at the time when treatment for syphilis will be far more likely to check the trouble than tonsillectomy

Nine of 13 patients had some plausible explanation of their rheumatic fever besides streptococcal infection. In this group of 13 patients were 2 in whom the cardiac condition was almost certainly rheumatic, and 1 in whom it was impossible to decide whether rheumatic fever was responsible for the condition, although the patient had tabes dorsalis and may have had coincident rheumatic endocarditis with syphilis.

The history of heumatic symptoms may therefore, be no small part of the story of patient with syphilitic aortic valvulitis, and greater care should be exercised in ascertaining the clinical importance of the rheumatic factor This undertaking is by no means simple and syphilis may emerge from behind an apparently fair case of rheumatism, with the prompt recovery of the patient under treatment for the former I view of hat seem to be occasional false positive blood Wassermann reactions in patients with septicemia and subacute bacterial endocarditis, the production of "pseudosyphilis by the streptococcus with the production of "pseudorheumatism by syphilis, deserves fuller study

It is worth while to recall, too, the value of critical inquiry into the question of gonorrheal arthritis in patients who give history of rheumatism. This does not suggest that the valvular lesion is gonorrheal in origin, but that chronic gonorrhea with its prostatic complications is fertile source of rheumatic symptoms that may mislead the history-bound examiner int overlooking the underlying syphilis in case of aortic endocarditis. I considering the cause of an aortic murmur therefore the examiner should at least palpate the prostate before accepting history of rheumatism as of bonafide streptococcal or rheumatic origin, and hence the cause of the aortic lesion.

A high proportion of the patients, 120 (83 per cent) with full venereal history in this cross-section had had gonorrhea. Thirty-seven (20 per cent) gave histories of rheumatism of one sort or another Thirteen (7 per cent) gave a definite history of rheumatic fever or postscarlatinal arthritis. Of the 37 patients who gave a history of "rheumatism," 29 had had gonorrhea or syphilis or both, 23 had had gonorrhea, 19 had had both gonorrhea and syphilis, 18 could give no history of either 5 had had gonorrhea only 5 had had syphilis only 23 had had positive blood Wassermann reactions, 5 had positive spinal fluid, and 5 had neurological signs of syphilis. Of the 15 patients who had had definite rheumatic fever or postscarlatinal arthritis, in 4 the rheu-

Fig. 709

COINCIDENT VASCULAR SYPHILIS AND NEUROSYPHILIS. SEROLOGIC NEGATIVITY PROBLEM OF DIAGNOSIS OF MEDIASTINAL MASS. RECURRENT SYMPTOMS OF MEDIASTINAL PRESSURE CONTROLLED BY TREATMENT FOR SYPHILIS ANEURYSM WITH CLOTS (?)

Railroad man, aged fifty-two years, married.

Examined August 15, 1918.

Chief Complaint Hoarseness Recurrent attacks. First attack t enty three years before relieved by potassium iodid in eight months. Paralysis of the vocal cords fifteen years before, transient. Hoarseness recurred one week before.

Chancre thirty years before. Medication by mouth one year Potassium iodid for hoarseness. Rubs t elve years before

Dizziness, Nausea, Vomiting, Loss of Control of Legs Six months' duration.

Palpitation, two months.

Stabbing Pains, Knees and Shoulders, two months.

Examination Heart 1.5 by 8.5 cm Blood-pressure 100/72 both sides. Dullness left upper chest. Dilated veins

Larynx: Left recurrent paralysis.

x-Ray of Chest Tumor upper mediastinum.

Fluoroscopic: N pulsation.

Blood Wassermann Reaction Negative

Neurologic Examination: Fixed pupils, unequal, irregular Deep reflexes exaggerated.

Spinal Fluid Negative.

Treatment Six arsphenamin injections, mercury succinimid intramuscularly

Marked Improvement in all symptoms, though still hoarse.

Final Diagnosis on Clinical Grounds Aneurysm ith clot fixation.

Fluoroscopic Examination: No change

DISCUSSION

1 Apparently this patient had had at least one previous transient laryngeal paralysis. He had had prolonged relapsing hoarseness good ma y years after the period in hich it would be likely to be due to secondary stage, and there as no scarring to suggest gummatous laryngitis.

2. It seems possible that the recurring attacks had been due to recurring expansion of the aneurysm with associated exacerbations of mediastinitis and pressure phenomena, relieved by treatment, or by the fixation of the aneurysm from clotting

3 The long duration of the symptoms makes mediastinal tumor of other than syphilitic origin improbable

4 N urosyphilis, associated with the vascular picture, may easily have negative serology The picture wa not, however typical or advanced.

5 Unilateral pupillary inequality without fixation to light may be the result of aneurysmal pressure on the cervical sympathetic, or involvement of the nerve in mediastinitis and perivasculitis

matism followed gonorrhea (not necessarily immediately) and in 5 the rheumatism followed syphilis (not necessarily immediately)

Th Austin Flint Murmur.—The simulation of the murmur of mitral stenosis by the Austin Flint murmur has many times raised the question of mitral disease and rheumatic etiology in a case of syphilitic aortitis, for after all, the demonstration of mitral disease coincidently with aortic insufficiency is the critical point in the large majority of diagnoses of rheumatic aortic valvular disease. The remarks of Carter and Baker summarize this problem. They found typically characteristic Flint murmur present in 45 (50 per cent) of 70 cases, and in 4 found it to be associated with palpable thrill t the apex T quote them "It may be stated categorically we believe, that in the presence of conspicuous aortic insufficiency with greatly hypertrophied left ventri-

cle, the presence of the characteristic Flint murmur even when accompanied by a late diastolic thrill, call it presystolic if you will, does not justify the diagnosis of mitral disease except in the absence of all the criteria indicative of syphilitic disease and the presence of definite history of rheumatic infection and possibly previous attacks of recognized rheumatic endocarditis in the past and such clinical signs as increase in the intensity of the first sound at the apex and enlargement of the left auricle.

"This distinction cannot be too strongly emphasized. It has been forced upon us only after more than one humiliating lesson in the failure of the pathologist to confirm the clinical description in such cases.

Nichols (1940) in discussing differentiation of the Flint murmur insists on its presystolic time and "blubbering" or rumbling quality Kampmeier (1945) found it present in 16 per cent of 163 patients with insufficiency

Roentgenological Diagnosis—Aneurysm *versus* Tumor—From the Mayo Clinic experience it became apparent that one of the important practical differentiations in dealing with thoracic aneurysm is between this condition and tumor It is in the fluoroscopic differentiation of the two that the probable influence of perivascular and mediastinal incarceration of the sac in the surrounding inflammatory infiltrate reaches its greatest importance. Obviously by the roentgen ray if any enlargement whatever is disclosed, it appears as a tumor whose location may of course identify it correctly It is quite likely however to be indistinguishable from the lymphomatous tumors of the mediastinum, from mediastinal Hodgkin's disease, or lymphosarcoma, from malignant metastasis, and from substernal goiter

T these possibilities for confusion the following have been added: tuberculosis of the lung, rated by Kampmeier (1938) as the commonest error in descending arch aneurysms occluded bronchus with bronchiectasis; pneumonia or delayed resolution, sarcoma of the lung; bronchogenic carcinoma. Roesler (1943) includes also thymic tumor, teratoma, hydatid cysts, neurofibroma, ganglioneuroma, unilateral sacculated pericarditis, esophageal carcinoma and diverticulum, cold abscess of the spine. Roche, Steinberg and Robb (1941) report case of right-sided aorta with diverticulum confused with aneurysm.

The crux of the roentgenological differentiation, therefore, rests with fluoroscopic study But if pulsation is not apparent, the inclination is to diagnose a solid tumor (Fig. 713) occasionally allowing for the possibility of the aneurysmal sac fixed by intramural clotting (Fig 706) Our study indicates that this point of view is distinctly fallible and that the entire picture may be transformed by a short therapeutic test, which by resolving the mediastinitis and perivasculitis, permits the pulsation of the tumor to become visible under the fluoroscope (Fig 707)

The Therapeutic Test for Aneurysm *versus* Mediastinal Tumor—The therapeutic test for the diagnosis of aneurysm deserves much wider employment than it apparently receives, and should be particularly insisted on by the roentgenologist before he passes judgment on the character of a mediastinal shadow Nothing is sacrificed in inoperable cases by applying this test, either with or without a negative blood serologic reaction. Such a test must, of course, be begun with mercury and iodide, to avoid the risk of rupture from a too abrupt weakening of the wall, but in small tumors this preparation may be confined to four or five weeks, and three more weeks of small doses of neoarsphenamine or mapharsen will usually demonstrate pulsation if it is likely to appear This result is not, however invariable, and since little is to be lost at the present time in the relatively hopeless outlook of a malignant mediastinal growth by a delay of a few more weeks, the test may be prolonged

Fig. 707

THE CONFUSION OF AORTIC ANEURYSM WITH MEDIASTINAL TUMOR. INFLUENCE OF TREATMENT ON THE RESOLUTION OF PERI-AORTITIS AND MEDIASTINITIS, MAKING POSSIBLE THE DEMONSTRATION OF PULSATION BY x-RAY

Mechanic, aged forty-seven years, married.

Examined June 11, 1919.
Chief Complaint: Pain in the chest, especially right shoulder. Worse on exercise.
Mild Dyspnea. Slight Wheezing.
Penile Sore twenty years before.
No Secondaries.
Examination:
Heart left border 7.5 cm.
Heart sounds muffled, no murmurs.
Impaired resonance, prolonged expiration right upper.
Abdomen negative.
Knee-jerks absent.
Blood Wassermann Reaction Negative.

***x* Ray of Chest:** Mediastinal tumor probably aneurysm.
Fluoroscopic Examination: Non-pulsating, non-expansile tumor of mediastinum.
Sent for Therapeutic Test with Clinical Diagnosis of Mediastinal Gumma.
Treatment: Two weeks of rubs and potassium iodid followed by arsphenamin.
Pain in Shoulder Gone after second injection.
Able to Walk Any Distance after fifth injection. Wheezing gone.
Fluoroscopic Re-examination after sixth arsphenamin injection reports
Aneurysm of the Aorta; expansile pulsation.

DISCUSSION

1. *Note the paucity of physical findings.*
2. The fixation of the walls of an aneurysm by clots is more generally recognized as a factor in diagnosis than is its incarceration in the infiltration of a peri-aortitis or mediastinitis.
3. Cases of this type are at times treated with *x*-ray on a presumptive diagnosis of lymphosarcoma.
4. The application of a therapeutic test for syphilis to all mediastinal tumors would yield a fair return of aneurysms and gummatous mediastinitis. This should be an invariable practice before the patient is given up as beyond help.
5. The presence of palpable glands (Fig. 718) does not establish the malignant character of the process. They are not uncommon in mediastinal syphilis. A pathologic examination of such a gland may help to demonstrate, but does not eliminate malignancy.
6. On the other hand it must not occasion surprise if a therapeutic test fails, for there are cases in which it is impossible to distinguish clinically between syphilitic and malignant lesions of the mediastinum.

and roentgen ray treatment may be coincidently applied, if pulsation be used as the chief test for aneurysm.

Symptomatic Positive Test.—When marked symptoms accompany the lesion, they are often a fairly sensitive guide to the progress of the test, and the patient may notice distinct improvement in all his symptoms, especially the pain, dyspnea and hoarseness, if the cords are affected, some time before the tumor begins to show signs of pulsation.

False Positive Therapeutic Test.—While a positive therapeutic test is indicative of syphilis if signs of aneurysm are subsequently identified in the tumor, caution must be used in interpreting reduction in size or symptoms of mediastinal masses in which no pulsation is detected after reasonably prolonged treatment (two months). The influence of arsphenamine on the infiltrates of Hodgkin's disease and glandular tuberculosis may lead to a false diagnosis of syphilis from nonspecific effect, which will be reversed later by the ultimate outcome. For this reason, if these questions are raised, a soluble mercurial salt alone or inunctions should be used for a period of from four to six weeks before an interpretation is made. If the result is negative, the arsenical may then be continued for its nonspecific effect, if desired.

The Electrocardiogram in Syphilitic Cardiovascular Disease.—Electrocardiographic examination occupies a paradoxical but extremely important position in dealing with cardiovascular syphilis. It is the most valuable means

for determining the functional state of the myocardium, its need of treatment and its ability to withstand both toxic and therapeutic effects, especially those of induced fever (Lieberman and Katz, 1940). We have seen that heart muscle and conduction disturbances are rarities of the first order in secondary syphilis. The classified findings of Willius in the Mayo Clinic survey are given in Fig. 708. Abnormalities of the T wave and QRS complexes indicative of ventricular myocardial disease are foremost.

Juster and Pardee in an electrocardiographic study of 80 patients with syphilitic aortitis with ten autopsies found 85 per cent to present abnormalities of the T-wave and in 20 per cent this was of coronary type. The T-wave was abnormal in only 38 per cent of those without the valve lesions. Their autopsy study apparently connected the abnormality of the T-wave with the encroachment upon the lumen of the coronary orifices by the syphilitic disease in the sinuses of Valsalva. The greater frequency of the T-wave changes in the group with aortic insufficiency they believe is due to the fact that in these patients the aortitis involves the region of the valves near which the coronary arteries originate. For this reason, abnormalities of the T-wave in syphilitic aortitis should be viewed as an indication of serious coronary involvement but not necessarily as an indication of myocardial pathology. The grave prognostic significance of T-wave negativity in Lead I was repeatedly pointed out by Willius in the Mayo Clinic material. In Willius' later study summarized in Fig. 708, the very low incidence of electrocardiographic abnormality in cases of aneurysm is striking and in the main to be expected because of the relative exemption of the coronary orifices in the uninvolved aortic sinuses. Here in all probability lies one of the principal reasons for the better prognosis under treatment of aneurysm as compared with aortic regurgitation in our observation. Wood and Wolferth, and Parkinson and Bedford have identified electrocardiographic changes in proportion of cases of angina pectoris with coronary occlusion attributed in theory to ischemia of the heart muscle but not diagnostically significant. Smith and Blackford (1938) found the following changes to occur significantly more often in 108 patients with syphilis than in 300 patients with other types of heart disease: intraventricular conduction defect; left axis deviation; low voltage of T-wave. ST segment deviation. The occurrence of progressive increase in QRS slurring with decreasing voltage of the T-wave in the serial tracings was a most accurate and ominous sign of rapidly progressing fatal disease. Left ventricular preponderance and anterior wall infarction patterns are most frequent (Cole and Bohning, 1941).

Fig. 708.

ELECTROCARDIOGRAPHIC FINDINGS IN 90 CASES OF SYPHILIS OF THE VASCULAR SYSTEM

	Cases.
Abnormalities T wave [illegible]	23
[illegible]	22
[illegible]	17
[illegible]	16
[illegible]	10
[illegible]	10
[illegible]	9 (3 early)
[illegible]	5
[illegible]	3
[illegible]	2
[illegible]	11

Other electrocardiographic changes produced by syphilis and particularly by the arsphenamines are considered on pages 908, 925 and 945.

The Diagnosis of Peripheral Vascular Syphilis.—The manifestations of syphilis of the peripheral vascular system have been summarized in the discussion of pathology (page 903). Their clinical diagnosis is based largely on incidental recognition of the syphilis or of some manifestation which, in the absence of a positive serologic reaction and a good history, can still be interpreted as presumptive evidence of syphilis.

Syphilitics, like other patients with cerebral vascular disease, may exhibit such symptoms as fainting attacks, loss of memory hemiplegia and aphasia. The well-known tendency of syphilis to produce obliterative endarteritis as one of the fundamental pathologic changes which underlie



Fig. 709 —Ulceration and gangrene due to syphilitic obliterative endarteritis.

A young married carpenter ged thirty-fiv years, developed pain in the right little toe three years befor examination in the clinic. The skin came off and the toe turned blue. It finally healed. Then the right second toe turned blue and became gangrenous to the second joint. The whole toe was removed. There was no further trouble for nearly two years, and then the great and third toes of the right foot and the second toe of the left foot became affected in the same way The process ppeared in the fingers soon after involving the first on the right hand and the first and second on the left. Ther were no attacks of vasomotor spasm. The finger simply became discolored and the end became sore and dropped off, leaving the nail deformed. There was little discoloration or change in the foot.

At the time of examination the great toe of the right foot presented several sloughing punched-out ulcers. There were ulcers on the dorsum of the right third toe and left second toe, with cyanosis. The affected fingers also showed some ulceration.

The patient did not give history of either yphilis or gonorrhea. The wife, ho was in an insane hospital, had had tw miscarriages and tw pparently healthy children.

Examination failed to disclose any explanation of th process except the presence of strongly positive blood Wassermann reaction. The urine wa normal, the heart negative The blood-pressure, however as 180/84

Treatment resulted in the healing of all the ulcers xcept that of th great toe. Pain for time became more marked and then somewhat relieved, but still present. The patient neglected treatment and wa subsequently heard from indirectly as in another hospital with gangrene of the great toe, and doubtful positive followed by negative blood Wassermann reaction and negative spinal fluid.

Did this man hav syphilitic endarteritis? W have seen an almost identical case in somewhat younger man in whom not even syphilis could be advanced probable etiology

Against the vasomotor type of Raynaud' disease is the absence of history of paroxysmal spasm and temporary relief This process w slowly progressive

Against thrombo-angiitis obliterans would be the absence of migratory stage the absence of nodosities along the vessels, the invol ement of the hands.

No mention is made however of the condition of the nterior nd posterior tibial arteries, bvious and inexcusable versight on the part of the examiner hich makes complete differentiation in retrospect impossible

the clinical manifestations of the disease leads to an interpretation of any vascular symptom or accident as syphilitic *per se* provided it occurs in conjunction with syphilis. The question of direct etiology is exceedingly difficult to prove clinically nd there is little about the peripheral vascular lesions as such on hich to make the diagnosis. Arteriosclerotic changes are undoubtedly

associated with syphilis, but report of the percentage of positive Wassermann reactions obtained in cases of hypertension, for example, would give little clue to the proportion traceable to true syphilitic sclerosis.

Such an analysis has been attempted by Horine and Weiss (1930) for the American Heart Association symposium. The review of the literature emphasizes the wide divergence of opinion on this question. A number of the older reports rate syphilis high as causative influence Mattei and Tolson (1927) found syphilis the only etiologic factor in 14 per cent of 210 patients with hypertension. Stone and Van Zandt found syphilis in 28.3 per cent of 436 patients with hypertensive heart disease. Horine and Weiss point out that many of the prevailing estimates are determined, not by the influence of syphilis in the production of hypertension but by the frequency of syphilis in the clinical material studied. They therefore employed control series of 2000 nonhypertensive patients of similar ages and economic status.

Horine and Weiss concluded that the incidence of syphilis in their 600 patients with essential hypertension was essentially identical with that in the control group and that accordingly syphilis has no material etiologic bearing on essential hypertension. While investigations based purely on serological tests may be thought of as vitiated by the well-recognized frequency of seronegativity in some aspects of peripheral syphilitic vascular disease, our experience tends to bear out Horine and Weiss contention. Hypertension is not necessarily part of serious syphilis of the vascular

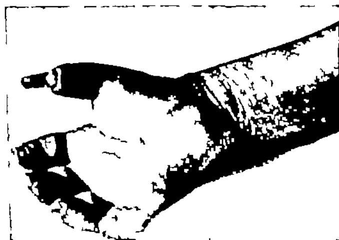


Fig. 710.—Gangrene from syphilitic (?) thrombosis of principal arterial trunk in syphilitic child. (Courtesy of Dr J C. Gittings.)

system, as is apparent from the really very moderate tensions exhibited in cases of advanced syphilitic aortitis and aneurysm with pronounced coronary sclerotic signs. Moreover as Elliott points out, syphilitic patients are not immune from the action of nonsyphilitic causes of hypertension. On the one hand, permanent reductions of arterial tension under treatment for syphilis undoubtedly do occur and the reductions are marked enough and lasting enough to give the impression of positive therapeutic test. On the other hand, so little is known of the etiology of essential hypertension, and it may be influenced from so many directions, that conclusions such as this are unsafe.

Peripheral vascular changes resulting in gangrene likewise present little that is distinctive of syphilis either clinically or pathologically (Figs. 709 and 710) One differential point, however we have found useful. If at the time of examination the patient has had repeated vasomotor spasm, in which the affected fingers or toes first blanch and then become suffused and swollen, or if he can give such history the condition is very unlikely to have syphilitic etiology The slowly but steadily advancing peripheral sclerosis with gradually developing pallor and coldness, blueness, and finally ulceration, is the type more often associated with syphilis, although of course this type may likewise be associated with arteriosclerotic changes secondary to age, diabetes, Buerger syndrome, and so forth.

The examination of tissue in suspected cases of syphilis for endarteritic changes is, in our opinion, unconvincing so far as syphilitic etiology is concerned. Aside from the fact that the bi-

opey wound may not heal and may force an amputation, endarteritis alone, especially in the skin, does not make diagnosis of syphilis, for exquisite examples may be seen in other conditions of as yet completely unknown but certainly nonsyphilitic origin. Buerger believed that the type of peripheral arteritis which he described, thrombo-angiitis obliterans, could be histologically differentiated from other obliterative lesions of the arterioles. The migratory character of the process in the Buerger syndrome is an important differential point.

The Therapeutic Test in Peripheral Vascular Syphilis.—The therapeutic test of so much value in the differentiation of syphilitic inflammatory lesions of the aorta and aortic valves has relatively little value in the differential diagnosis of peripheral vascular scleroses. The clinical changes which they present do not occur until the very end of the pathologic process, namely, the local or impending death of the affected part, or fibrosis which is practically not at all responsive to specific treatment. The resort to iodides, which is rational therapy in such cases, is not means of demonstrating syphilitic origin, for the drug is quite as effective, or rather more often as ineffective, in vascular conditions other than syphilis. Among the case reports is included an example of the nearest approach to a positive therapeutic test that we have been able to obtain in fully established case. It is quite possible that earlier arousing of suspicion at the time when tingling and pallor first appear with the recognition and vigorous treatment of the syphilis at that time, might result in complete arrest of the process. W have been dissatisfied with the results of therapy in intermittent claudication associated with syphilis.

Herrmann has used negative pressure in 5 syphilitic cases of peripheral vascular disease with benefit. Johnson (1941) described the case of a patient with severe Raynaud's symptoms, ulcers, scleroderma and sclerodactylia who obtained very little transient improvement after bilateral removal of the stellate and second dorsal sympathetic ganglia in 1932. The symptoms gradually became worse. In 1933 antisyphilitic treatment was instituted following which she had complete relief from Raynaud' symptoms through 5 winter seasons. Among the treatments which have proved useful in Buerger or Raynaud' disease are Buerger-Allen vascular exercise, diathermy, sitz, contrast, and whirlpool baths, tissue extract (*e. g.*, deproteinized pancreatic tissue extract), pavaex pressure-suction boot treatment, Sanders oscillating bed, intermittent venous hyperemia, vasodilating drugs (*e g* papaverine, choline compounds, etc.), mecholyl iontophoresis, sympathetic ganglionectomy periarterial sympathectomy (arterial resection), calcium orally 5 per cent sodium citrate or hypertonic saline solutions (3 per cent) intravenously and typhoid vaccine fever therapy

Clinically then, the recognition of syphilitic peripheral scleroses is a matter of exclusion of all other etiologic factors. Among the possibilities to be eliminated in cases presenting gangrene are diabetes, senile arteriosclerosis, infectious thrombosis and embolism Buerger's thromboangiitis obliterans, and the action of poisons especially damaging to the vessels, such as lead. Moreover obliterative endarteritis of fairly large vessels of absolutely undemonstrable etiology is known to exist, so that there remains a loophole through which any given case may escape If therefore an arterial obliteration with gangrene appears in a patient in whom a coincident syphilis can be demonstrated, treat the syphilis but suspend judgment on the diagnosis. Fig 700 is a good example of a strongly suggestive but not proved syphilitic etiology

The Diagnosis of Pulmonary Arterial Disease.—I 1917 Warthin reviewed the literature of this rare manifestation of syphilis in connection with case in which he demonstrated *Spirochaeta pallida* in the all of the aneurysm which had developed in the left upper division of the pulmonary artery The egg-shaped mass ith its surrounding adhesions appeared in the roentgenogram as mass in the body of the lung extending from the second to the fourth rib. The symptomatology included repeated pulmonary hemorrhages ithout other symptoms of tuberculosis or of aneurysm the signs included diastolic pulsation visible in the neck, marked diastolic murmur in the third intercostal space transmitted upward nd across. The blood Wassermann reaction as positive. Before death, which occurred from hemorrhage, to-and-fro murmur t the apex and marked difference in pulse bet een the two arms were recognized. The clinical diagnosis as gumma of the lung. In remarkable case in Stokes's practice seen h Wolferth in cardiological consultation, young man of twenty-four following pneumonia with markedly delayed resolution (seven week) was found to have a positive blood Wassermann re-

action, without history of syphilis or gonorrhea. Some months following his pneumonia he developed nodulo-ulcerative cutaneous lesions and in the examination at the time the heart was entirely normal but the patient showed signs slightly suggestive of prenatal infection. The cutaneous lesions responded to arsphenamine, mercury bismuth, iodide, and bismuth arsphenamine sulphonate, but after lapse of two years on returning for observation, systolic murmur over A2, systolic and diastolic murmur over P2 at the base of the heart were recognized. Several examinations by different consultants had established the normality of the cardiovascular system in the interval between the pneumonia and this first appearance of signs. The basal double murmur as detected by Wolferth, was markedly influenced by respiration and the diastolic phase began with the second sound and faded off in the latter part of diastole. Fluoroscopic examination showed definite prominence of the curve of the pulmonic artery with striking pulsation in comparison with the lesser pulsation of the aortic knob above. Wolferth believed the findings suggestive of pulmonary ring dilatation with aortic syphilis and probable syphilis of the pulmonary artery

For additional reports see page 903 (pulmonary aneurysm) including Segal 1940 (gummatous arteritis) and Allen and McCracken (1940).

THE TREATMENT OF SYPHILITIC CARDIOVASCULAR DISEASE

One of the few pleasures one derives from rewriting a textbook lies in the appreciation which it brings of the march of events toward rational solution. In no field of syphilis more than the cardiovascular is this rearranging into an ordered pattern of the elements of a crazy-quilt patchwork puzzle more apparent and acceptable. The original cardiovascular treatment section of this work was perforce confined to a somewhat broken array of landmarks scattered like boulders about a field. It is now possible, with our growing knowledge to place these boulders at least in a wall and to describe almost in a paragraph the fundamental principles now recognized as applicable to treatment of the syphilitic heart and great vessels.

The Literature.—Much of the literature of methods and results in treatment still preserves the impressionistic quality of individual, statistically uncontrolled or uncontrollable experience. Among notable contributions toward exactitude must be mentioned the direct studies of the effect of the arsphenamines on the heart (Reid, Koldel and Moore, Wilson, Wile, Wishart, and Herrmann). On the clinical side there has evolved an increasingly clear-cut and favorable opinion regarding the use of the arsphenamines, in properly selected cases, in aortitis and aneurysm. Notable contributors to the problem include Braun, Schottmüller Schlesinger, Horder Kothny and Müller-Deham, and the authors included in the recent symposium in the Dermatologische Wochenschrift, including Citron, Galewsky Klech, Lesshke, Ritter and Schlesinger and the observations of Conybeare, on arsphenamine in the treatment of aneurysm. The American contribution, particularly to the evaluation of treatment effect, has been striking one, including the American Heart Association symposium papers of Hines and Carr, and Moore and his associates. The paper by Moore, Danglade, and Reisinger, to which reference is constantly made, was at the moment the most complete in the literature and marks as substantial an advance in knowledge as did Moore and Kemp papers on early syphilis. Since the advent of mapharsen particularly fear of the arsenical is notably diminishing, and its earlier use in fuller dosage is being encouraged. W personally hesitate at too much relaxation of precaution at this point, as "hurry up rather than wisdom, and still counsel the cautious though not dilatory approach by preparation. The papers by Harlow Brooks and Wile present the more conservative viewpoint and the latter conception of therapeutic paradox may now be regarded as established, although the means of avoiding it without the necessary exclusion of the arsphenamines are open to debate. A well-defined body of opinion is developing in opposition to the use of the arsphenamines in angina pectoris and coronary sclerosis (Schlesinger et al., Handbuch) to which it was possible in the first edition of this work to present well-defined theoretical objections. The duration of life and comfort of the patient have been substantially advanced and the period of discouragement and reaction, in which we shared following the recognition of the unfortunate consequences of therapeutic shock and paradox from overintensive treatment, has given way to renewed hopefulness.

The Accepted Principles.—In Fig. 711 we have attempted to summarize from the foregoing literature as well as our personal experience what we be-

lieve to represent the current opinion on accepted principles in the treatment of cardiovascular syphilis. The details should be read with care.

Treatment Is Worth While—It has long been accepted that the use of mercury and iodide in syphilitic cardiovascular disease improves to some

Fig 711

SOME PRINCIPLES IN THE TREATMENT OF CARDIOVASCULAR SYPHILIS

1 Effective modern treatment of primary and secondary syphilis reduces the frequency of later cardiovascular involvement.
2 Complete arrest of an early cardiovascular involvement is possible.
3. With proper selection and proper management, treatment of later cases is worth while. It prolongs life and increases comfort and effectiveness.
4. All reactions to treatment should be avoided.
5. Treatment must be individualized for each patient. The treatment of each phase or type of involvement is a special problem. In general, more intensive and fast-acting methods are appropriate to early (uncomplicated) syphilitic aortitis. Later syphilis of heart and aorta must be approached with great caution even though subsequent treatment may be both intensive and prolonged.
6 The arsphenamines are intrinsically toxic for the syphilitic cardiovascular patient this is most true of 606, least of mapharsen.
7 None the less, they can and should be used because:
   (a) Toxicity can be controlled by dosage and selection.
   (b) Neoarsphenamine and bismuth arsphenamine sulphonate have little or no toxic effect in proper dosage. Mapharsen has least of all.
   (c) The results symptomatically are better with than without, especially in aortitis and aneurysm (relief of pain, dyspnea, etc)
   (d) The life expectancy is increased if proper selection and technic prevail.
8. But therapeutic shock and paradox are grave realities.
9. They can be avoided by
   (a) Completely examining the patient, including teleroentgenogram, fluoroscopic and electrocardiographic study before beginning treatment.
   (b) Never giving a patient with syphilitic cardiovascular disease an arsphenamine at the outset except in minute doses.
   (c) Never giving a large dose of an arsenical at any time
   (d) Beginning the treatment of decompensated or badly damaged hearts with mercury and iodide rather than bismuth or arsphenamine (exception, see bismuth arsphenamine sulphonate).
10. Marked coronary and myocardial disease is a relative but not absolute contraindication to the arsphenamines.
11 The patient with a syphilitic heart should be intelligently managed from the standpoint of both the syphilis and the heart condition, not from that of either alone
12. Cardiovascular disease takes precedence over all other complicating forms of syphilis in determining treatment procedure in any given case
13. Decompensation is a specially grave complication, to be avoided at all cost It disproportionately reduces expectancy and restricts the possibility of treatment after it has occurred.
14. Digitalis is less active in the syphilitic heart than in other forms of heart disease and especially so in the Negro.
15 Cardiovascular patients with fixed positive serological reactions should not be treated merely to reverse the blood test.
16. Treatment in all cases must be prolonged over several years.

degree the outlook of the patient. The younger clinicians now coming into maturity and the general practitioner unaware of the pitfalls awaiting him, witnessed in the years from 1919 to 1921 in this country the reaction against the use of the arsenicals in the then customary large doses, the impression of which is still so strong in the minds of conservative observers that it will

require much convincing to induce them to readmit arsenical derivatives to their confidence in the treatment of cardiovascular syphilis. This period of overuse and misuse established beyond all question the reality and dangers of therapeutic paradox and therapeutic shock.

A reconsideration of the logic of the situation a differentiation on physiopathologic grounds of cardiovascular syphilis into various types of impairment a dogged persistence and confidence in occasional good results on the part of certain observers, and some blind luck, led to the development of systems of treatment, among them the one which first attracted our attention, that of Kothny and Müller Deham in which small ascending doses of neoarsphenamine were demonstrably well tolerated by a large proportion of patients and with decided benefit. It has become gradually apparent that therapeutic shock, at least, is as much if not even more a matter of dosage than of selection of drug, and that it is possible so to use an arsenical in the treatment of cardiovascular syphilis as to avoid disaster immediate or ultimate. From this principle as a base, a number of observers named in the previously listed literature, like ourselves, have developed technics for the use of arsenicals in practically all phases of cardiovascular syphilis which are now in process of evaluation but which a reasonably experienced observer can, we think, unhesitatingly subscribe to as representing gains over the older methods As Moore Danglade, and Reisinger observed in their own material, it is very much more difficult to secure statistical data which will evaluate the incidence of therapeutic paradox. The principal approach to the problem at the present time must be in the estimation of gains in life expectancy and the results in this field are reviewed on page 959 under Prognosis.

Intrinsic Arsphenamine Toxicity —A substantial advance was made by Reid and subsequently confirmed by Wilson, Wile, Wishart and Herrmann, in examining electrocardiographically the effect of the arsphenamines on the heart. Arsphenamine cardiac collapse, which is discussed under Treatment Reactions, was emphasized by Moore and Keidel and by our own experience as source of disaster in treating cardiovascular syphilis, and they advanced the hypothesis that the effect was due to the induction of ventricular fibrillation by the drug Reid (1945) found that the effect of moderate doses of arsphenamine was to produce first, certain unimportant changes due to stimulation of the vagus, and secondly certain alterations in the QRS complex and the T wave indicative of alteration in conduction in the ventricular tissues. The aggregate effect of these changes in heart damaged by syphilis or as Reid says, "in bad metabolic condition, is to predispose to ventricular tachycardia and ventricular fibrillation through prolongation of the conduction period and shortening of the refractory phase. The ectopic auricular tachycardia is, of course, serious, the ventricular fibrillation fatal. Fortunately such effects must be rare.

Wilson *et al.*, in case of death following 0.3 Gm. arsphenamine in patient with syphilitic myocarditis and complete right bundle branch block, demonstrated an abnormal idioventricular rhythm following the drug Two other patients with aortic syphilis developed diphasic complexes suggesting incomplete bundle branch block with transient T-wave changes but greater persistence of the QRS changes. Similar treatment produced no changes in the electrocardiograms of five other patients with aortic syphilis, and intensive arsphenamine therapy in 20 patients with primary and secondary syphilis produced no electrocardiographic abnormalities.

Tung and Hu (1940) studied serial electrocardiograms in 22 cases of syphilitic aortic insufficiency to whom neoarsphenamine was administered. Mild or moderate change in the R-T or S-T segments or in the T deflections occurred 11 times out of 16 examinations in 5 cases. In 2 cases there were marked changes in the ventricular complex. From their observations the authors conclude that their study serves as warning that, if used indiscriminatingly the intravenous injection of neoarsphenamine may jeopardize, at least temporarily the coronary circulation, and possibly the life of the patient. Geiger and Sadusk (1948) performed serial electrocardiograms on 23 patients with early syphilis before, during, and after massive dose (five day drip) arsenotherapy In 21 of the experiments significant abnormalities during or shortly after treatment (*e g* diminution of the amplitude of the T wave in all leads, frequent inversion of T in all leads other than

the third, *etc.*) were observed, which findings returned to pre-treatment control values within a few weeks after treatment was discontinued.

Fig. 712

"TUMOR OF MEDIASTINUM. UNFAVORABLE PROGRESS UNDER TREATMENT. DEVELOPMENT OF PULSATING TUMOR, SHOWING MASS TO BE AN ANEURYSM

Man aged forty-eight years, married, laborer

Examined 6/19/18.
Gonorrhea Twenty-five Years Ago. No history of chancre or secondaries.
Duration of Symptoms: Eighteen months.
Symptoms:
Pain in left shoulder
No cough.
No voice changes
Abscess (?) over left scapula opened eighteen months ago.
Physical Signs:
Restriction of movement, left chest.
Dilatation of superficial veins.
No visible tumor
No *murmur thrill, pulsation, or tug.*
Palpable glands, both axillae.
Scar over left scapula.
Roentgenographic and Fluoroscopic Examination: No *pulsation.*
"*Tumor of mediastinum, probably sarcoma.*"
Serum Wassermann reaction moderately positive.
Treatment: Rest in bed one week with *Mercurial preparation.* Six inunctions, 4 injections mercury succinimid, potassium iodid by mouth.
Arsphenamin. 0.3 gm., 0.4 gm., 0.5 gm., 0.5 gm. at weekly intervals.
Relief: Loss of weight 10 pounds in six weeks.
Pulsating Tumor appeared with third injection arsphenamin at inner border left scapula and increased rapidly in size. Complete relief from pain.
Tracheal Tug Appeared. Aneurysmal pulsation now demonstrable by fluoroscope.

DISCUSSION

1 The roentgenographic diagnosis of malignancy was supported by palpable glands.

2. Not every mediastinal mass that does not show pulsation is a solid tumor nor is every mediastinal mass with an associated partial positive Wassermann reaction a manifestation of syphilis. Exploration has demonstrated sarcoma pathologically In general, however a therapeutic test should precede exploration.

3 A therapeutic test for syphilis may demonstrate an aneurysm previously unrecognizable. Such tests must be made with a prolonged mercurial and iodid preparation.

4 Two weeks of inunctions is not an adequate mercurial preparation. Four to six weeks is better

5 The rapid tissue change and the possibl serious effects induced in late syphilitic lesions by modern treatment for syphilis are well illustrated by this case. This patient should have had several weeks of rest in bed on mercurial and iodid preparation, with arsphenamin later rather than a therapeutic shock from such a rapid-acting vasculotoxic drug as arsphenamin at the outset. The initial dosage of arsphenamin was excessive. We have learned to prefer neo-arsphenamin 0.05 to 0.4 gm. in ascending dosage with weekly intervals.

6 The change in the roentgenologic and physical findings which appeared after the third week suggests late healing rather than early Herxheimer effect. The pulsation, visible tumor etc., previously unrecognizable, appeared presumably with the weakening of the vessel wall and the resolution of the peri-aortitis and mediastinitis which had caused the fixation and supported the vessel.

7 Provocative procedures may be dangerous in mediastinal conditions.

8. Treatment seldom produces much visible change in aneurysms. Occasionally, however they may resolve completely

Therapeutic Shock and Paradox as Illustrated by Case Records, in Aneurysm.—The degree of responsibility of therapeutic shock and paradox for serious or fatal outcomes in the treatment of the syphilitic heart is still somewhat a matter of guesswork, owing to the nonvisibility of the lesion. In the case of aneurysm however in the days of our earlier mistakes, we watched

Fig. 713.

NO PULSATION FLUOROSCOPICALLY. ANEURYSM VERSUS SUBSTERNAL GOITER. DEATH FOLLOWING FIRST ARSPHENAMIN INJECTION. NECROPSY SHOWED INNOMINATE ANEURYSM

Banker aged sixty-two years, married.

Examined 6/19/1917

Chief Complaint. Tabes and right subclavian aneurysm.

Chancre and Secondaries thirty-eight years before.

Substernal Pain and Bruit Over Sternum six years before. Diagnosed aneurysm. Right arm swelled up.

Tabes Diagnosed and Treated three years before. T courses of four and three weeks treatment each.

Present Symptoms. Precordial and substernal pain, lost voice on tipping head back.
- Sense of pressure in throat.
- Right arm still swollen.
- Pains in legs and other lower cord signs of tabes.

Physical Examination (Pollock)
- Slight ptosis of the right eyelid.
- Palpable thickening of right supraclavicular region, like lymphangitis.
- Superficial veins of upper chest marked, especially right.
- Suprasternal pulsation, no tracheal tug.
- Central dulness of upper sternum, with bruit.
- A_2 very sharp. Pulses synchronous.
- Heart enlarged to the left.
- Blood-pressure, right 190/120; left 170/120.
- Reflexes delayed.

Blood Wassermann Reaction Negative.

X-Ray of Chest. Large mediastinal shadow most marked on right. Arch either dilated or pushed over by mass. Fluoroscopic to differentiate aneurysm or substernal goiter; suspicious for latter.

Fluoroscopic Examination (Carman): "Can't see pulsation, right side mass, but must be aneurysm.

Sent for Antisyphilitic Treatment. Arsphenamin 0.2 gm. (he had had it three years before without incident).

Nausea, loss of appetite, malaise. Five days later he developed
- Stertorous breathing.
- Marked substernal pain.
- Marked hoarseness.
- Signs of pulmonary congestion.

Died two days later with signs of cardiac failure.

Necropsy: Anterior mediastinal tissues fatty and hyperemic. Fibrinous pericarditis. Large mass tumor-like 9 by 15 cm. upper anterior mediastinum. Sternal end of clavicle eroded. Esophagus and trachea pushed aside 5 cm. Left subclavian and carotid arteries pass along the left side, right subclavian and right common carotid emerged from it. Aneurysm of innominate, aortic arch pushed below and to the left of the mass. Many small aneurysmal pockets in the aortic wall.

The aneurysm eroded the anterior wall of the trachea, opening 1 cm. in diameter. The sac contained laminated pinkish-yellow clot, with central core of postmortem clot.

Discussion

1. It is apparent that an innominate aneurysm with clot fixation may closely simulate mass, such as substernal goiter. The previous diagnosis of aneurysm by competent internist was probably of some assistance. This clot fixation probably explains the absence of fluoroscopic pulsation.

2. At necropsy the mediastinitis and perivasculitis could be recognized. They were probably accentuated by Herxheimer reaction in the tissues following the arsphenamin.

3. This patient was treated several years before growing experience had taught us the value of mercury and iodid preparation. He had, of course, enough other pathologic changes to have caused his death, including the pericarditis which escaped clinical recognition and thrombus almost occluding the openings of the right common carotid and subclavian arteries.

4. At th age of sixty-two, iodid by mouth and few injections of mercury succinimid followed by mercury by mouth would probably have given this patient all the outlook possible under the circumstances, even had he not had the pericarditis.

with dismay and deep concern the rapid physical change for the worse with enlargement of the lesion that took place following the too-early too-intensive, or otherwise injudicious use of the arsphenamines. Figures 712 and 713 are strikingly illustrative of this complication.

Syphilis vs. Heart—Which to Treat First.—Still another group of problems vexing alike to internist and syphilologist during past years has been that of the relative importance, from the therapeutic standpoint, of the patient's syphilitic infection as compared with the state of his heart and vessels as a circulatory mechanism There are still two distinct groups in opinion on this matter Some observers, such as Wile take decompensation prior to treatment or at the time of beginning treatment as the dividing line in reaching the decision whether to initiate treatment for syphilis at once or to defer it. Wile (American Heart Symposium) especially if the patient has had previous thorough treatment, contends that the heart decompensating under such conditions is to be looked upon merely as a malfunctioning physical mechanism While this position seems eminently reasonable with the previous treatment provision inserted we believe it is too readily extended or altogether disregarded. The disposition of a number of clinicians is to claim the heart as a heart and to disregard its owner who has syphilis. The general rule that syphilis should be thought of as affecting unfavorably the structure and function of any organ once involved in which the process cannot be proved to be extinct, should be thought of in dealing with the decompensated syphilitic heart. Treatment for the two conditions, structural disease, and damaged function should go forward together the patient being placed at rest and digitalized, and otherwise, as will be presently described, treated as a heart case while the treatment for syphilis is cautiously initiated in accordance with the indications. Figure 720 dealing with the failure of cardiological methods until syphilological treatment was begun, is in effect a case report in support of this contention It is probably quite as often necessary to remind the practitioner and the syphilologist that the syphilitic patient with a heart complication and a positive serologic reaction must be managed as a heart case, as to remind the cardiologist and internist of the obverse of the situation.

The Preventive Value of Effective Modern Treatment in Early Syphilis.—We have seen that there is, in the course of early syphilis under treatment, a certain element of inevitability represented by perhaps ½ per cent of cases, in the incidence of cardiovascular involvement, regardless of the thoroughness of the treatment procedure. Fortunately the evidence collected by Moore and Kemp, by Moore Danglade and Reisinger by the Cooperative Clinical Group (1936) by Kemp and Cochems (1937) (Fig 715) and by Thompson, Comeau and White (1939) puts the matter in an even more encouraging light, and clearly demonstrates that what happens to the heart and aorta with respect to syphilis in the late years of the disease is the direct preventive responsibility of physician and patient in the period of primary and secondary manifestations Adequate treatment early can totally prevent cardiovascular manifestations late

The two first-named groups showed that of patients receiving from one to eight injections of an arsphenamine product, mercury being used not at all or less than one month, 9.0 per cent developed aortic lesions. Of the patients receiving one or two courses of arsphenamine with interim mercurialization, 5.0 per cent developed aortic lesions; while of 117 patients who had received three or more courses of arsphenamine and treatment with a heavy-metal preparation during the interim, not single one developed cardiovascular syphilis.

The Cooperative Clinical Group results are summarized in graphic form in Fig. 714

Kemp and Cochems very convincing demonstration is tabularly summarized from larger table in Fig. 715.

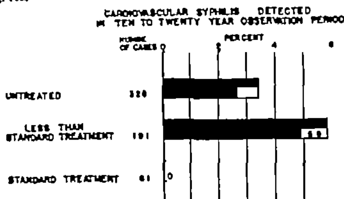


Fig. 714.—Probability of developing cardiovascular syphilis in treated and untreated syphilis. From Vonderlehr and Usilton, Ven. Dis. Inform. 19 396, 1938.

Thompson, Cesseu and White in fifteen to twenty-five year material showed though less clearly than the above studies, decline in cardiovascular syphilis with improvement in the intensity of what was at best only fair early treatment.

The Therapeutic Approach to Cardiovascular Syphilis.—As in all aspects of late syphilis, but perhaps more conspicuously in this field than in any other

Fig. 715.

EFFECT OF THE TREATMENT OF EARLY SYPHILIS ON THE INCIDENCE OF CARDIOVASCULAR SYPHILIS*

Amount of early treatment	Number of patients	Percentage with cardiovascular syphilis
None or very little	90	10 5
Inadequate	81	7 4
Adequate	240	0 4

After Kemp and Cochems Am. J Syph., Gonor. & Ven. Dis. 21 625, 1937

because of the sudden disaster that may punish a mistake or omission, the thoroughgoing appraisal of the patient is the first step to rational management. This appraisal should be sweeping and include all the patient s condition and resources, mental, physical, and material. A review of the situation by a cardiologist or a heart center is valuable and in many cases indispensable Certain of these considerations are discussed under special problems.

The basic physical matter for first consideration, both in the compensated and decompensated patient, is the state of the coronary and myocardial mechanisms. These, more than any other structures, limit the choice of treat ment agents and influence the prognosis. In estimating the myocardial situa

tion electrocardiographic studies are essential in addition to the experienced appraisal of the functional capacity of the heart muscle and the general state of the circulation. The gravity of inverted T waves in Lead I and of markedly aberrant QRS complexes should not be underestimated or evaded, and the risk of throwing such patients into serious condition by the use of an arsphenamine without prolonged preparation if not the desirability of its entire

Fig. 716.

EARLY ANGINA PECTORIS IN A YOUNG MAN WITH UNRECOGNIZED SYPHILIS. IMPROVEMENT UNDER TREATMENT ARREST OF THE PROCESS SHOWN BY SIX YEARS OF OBSERVATION

Machinist, aged twenty-nine years, married.

Examined 4/3/1917
Chief Complaint Gastric distress.
Heart-burn followed by exhaustion.
Pain in stomach runs into back and arms, especially left arm. Influenced by exertion.
History of Gonorrhea five years before.
N History of Syphilis.
Blood Wassermann Reaction Positive.
Positive on repetition.
Examination Moderate left ventricular hypertroph heart otherwise negative.
Blood-pressure 150/100.
Repeated, 132/80.
Nervous system *negative*.
x-Ray of chest, calcified area right upper
Electrocardiogram Rate 80 left ventricular hypertrophy
Consultant's Diagnosis *True angina pectoris* At his age probably syphilitic (W A. Plummer)
Treatment Begun Five injections neoarsphenamin, mercury succinimid intramuscularly inunctions.
Very Much Improved Only three attacks since treatment began. Weakness and dyspnea improved.
Septic Tonsils Removed.
Second Course of Treatment Very much stronger almost no distress on exertion.

Two More Courses Arsphenamin and Mercury 100 inunctions, 24 injections succinimid to date.
Blood Wassermann Reaction Fluctuates.
Spinal Fluid: Normal at first, developed a slight pleocytosis (10) year after treatment was begun. This as reduced to *normal and remained* so after 4 Swift Ellis treatments.
Arsphenamin Treatment Continued to 26 Injections.
Can Still Bring on Slight Attack by Exertion, but, on the whole, scarcely any disability
Repeated Cardiovascular Examinations have shown transient aortic murmur hich finally disappeared, leaving only the tambour second sound. Electrocardiogram negative.
The Patient Enthusiastic over the effect of mercury succinimid and sodium iodid intravenously which made him *feel* better than anything he had ever had. Wassermann permanently negative.
Total Treatment: Twenty-six arsphenamin injections, 100 injections mercury succinimid, 290, 30 *gr Hg* inunctions and 780 *gm.* sodium iodid intravenously Period of observation six years.

DISCUSSION

1 In sense the consultant took "long shot" t the diagnosis, but subsequent progress under treatment seems to support him. The improvement well advanced before the septic tonsils were removed.

2. This kind of therapeutic test is life insurance and is much more frequently justified than it is applied. With syphilitic background, or strong presumption, it is justifiable to treat an exceedingly early lesion such as this on suspicion.

exclusion from the treatment, must be most carefully weighed Personally we have tended to set down a high grade of myocardial involvement as a positive contraindication to the arsphenamines

Patients with syphilitic cardiovascular disease who present anginoid symptoms (see Fig 698) are coming to be accepted by an increasing number of observers as Schlesinger points out, and we have ourselves felt, as disqualified

for the arsenicals unless the most prolonged and painstaking preparation convincingly demonstrates both the reality and the permanence of their improvement. These statements apply full force to the later case and older patient. Undoubtedly there are exceptions in the case of younger patients with comparatively unimpaired cardiac and general physical reserves, as, for example in Fig. 716 but such occasional brilliant results do not offset the patient whose rapid relief of pain and spectacular improvement following the immediate employment of the arsphenamines may in six months or a year when the connection with his prematurely intensive therapy has been forgotten, pay the price in a rapidly failing heart and death from a therapeutic miracle. The return of the angina, the resort to surgery the increasing invalidism and eventual cardiac failure are still too familiar If the arsenicals are used at all in coronary cases, it must be in the minute doses appropriate to the worst and greatest rather than the least and most optimistic estimate of the damage already present, for necropsy repeatedly discloses in such patients a degree of involvement of the coronary orifices and obliteration of the vessels out of all proportion to the symptomatology during life.

The first breach of compensation is so serious as a warning of early fatal outcome that it must be accepted as indicating the most conservative procedure, and an avoidance of bismuth and the arsenicals at least at the outset. As the toxicity for the heart and general reaction-producing tendencies of newer drugs and agents, arsenical or otherwise decreases, this dictum may be modified.

Age while by no means infallible as a criterion, furnishes valuable clues to what may be expected in the form of resources and stamina under treatment. The patient who finally in his fifties, goes to the wall with a decompensated syphilitic heart, has very little recuperative power Much less can be expected of him in the way of treatment response than of the younger patient whose aortic murmur and evidence of syphilis are discovered while his heart muscle is still perhaps far from exhausted.

Appraisal of Treatment Tolerance.—It is extremely important, as Moore, Danglade, and Reisinger among others, have recently emphasized, to avoid all reaction to treatment in dealing with the syphilitic cardiovascular system. For this reason, all the considerations discussed in our chapters on reactions and complications and collateral factors, must be brought to bear. The patient in whose cardiac syndrome there is a marked element of renal insufficiency will tolerate a properly selected arsenical *in small doses better than mercury* or perhaps even bismuth. In hypertension the arsenicals in our experience are distinctly better tolerated than mercury and in some cases seem to produce, as in Fig 717 a definite if transient fall in blood pressure. In the earliest cases of aortic disease which we have dealt with a definite rise in blood pressure seems to occur between the first examination, in which no physical sign or only a systolic murmur was apparent, and the later examinations, after treatment, in which the process was supposedly showing healing sclerosis and had become stationary (Fig 719) In patients who present a coincidence of cardiovascular and visceral lesions as in hepatitis, the indications for the avoidance of treatment complications are much the same for both.

Coincident Cardiovascular and Neurosyphilis, as a Factor in Treatment.—In general we believe it is wisest to take the stand in a treatment appraisal, that the indications for the treatment of the cardiovascular phase of this combination should rule the decision.

Fig. 717

FLUOROSCOPIC DETECTION OF ANEURYSM IN THE ABSENCE OF OTHER SIGNS THAN THOSE OF HYPERTENSION (LATER AORTITIS) TEMPORARY REDUCTION OF BLOOD-PRESSURE UNDER TREATMENT FOR SYPHILIS. EXCEPTIONALLY LONG LIFE.

Housewife, aged fifty-eight years.

Examined 3/25/21

Chief Complaint: Debility rapid aging. Nervously distraught.

Marital History One miscarriage, two healthy children.

Swelling of Sternal End of Right Clavicle at age of thirty-two years. Supposed dislocation.

Seen by a Surgeon, Who, Without Comment, Gave Her Liquid Medicine to Take.

Examination: Heart enlarged to left.

Apex heaving Slight systolic blow at apex, not transmitted. Also heart at aortic area.

Aortic second accentuated.

Bony swelling right sternoclavicular juncture—Osteoma (?).

Blood-pressure 200/104. Repeated 198/100.

Nose and throat negative.

Urine negative.

Blood Wassermann Reaction Strongly positive. Evidently surprise.

Repeated, same result.

-Ray Clavicl negative.

N x-Ray Examination of th Chest at This Time.

Diagnosis, Syphilis. Essential hypertension. Slight anemia.

Treatment Begun Rest in bed, inunctions and potassium iodid 30 grains three times daily

Blood-pressure after third week in bed. 140/90

Neoarsphenamine Begun: 0.1 to 0.4 gm.

Blood-pressure after fourth week in bed. 120/78.

Up and Around. Four neoarsphenamine injections, mercury rubs, and iodid so far

Blood-pressure 130/88. (Patient up.)

Home on 40 inunctions.

Blood Wassermann Reaction still strongly positive.

Returns after five months for course of mercury succinimid and sodium iodid intravenously

Blood-pressure 168/96. Slight arrhythmia.

Re-examined After Another Seven Months with very little treatment.

Blood-pressure 168/90

Cardiac dulness 4.5 cm. by 13 cm.

No arrhythmia.

To-and-fro murmurs aortic area.

Capillary and Corrigan pulse.

Electrocardiogram: Diphasic T Derivation III. Right ventricular preponderance nodal premature contractions. Notched P wave in Derivation II.

Sent for x-Ray of Chest as part of the routine special cardiovascular examination.

Report: Aneurysm of the Aortic Arch.

Discussion

1. Observe that the surgeon who examined her in the pre-Wassermann days of clinical syphilology apparently made a diagnosis of sternoclavicular gumma and gave iodid. The first thought of her present examiner was anything but syphilis—osteoma.

2. This patient' aneurysm passed unrecognized by physical signs, through the entire period of her observation. She was closely studied by consultants, so that the lack of signs was not due to lack of skilled attention or to oversight.

3. Only the routine fluoroscopic x-ray examinations of the chest as part of the special cardiovascular examination by Willius revealed the aneurysmal lesion. There as no hoarseness, no pain, no significant dyspnea, and, of course none of the physical signs. \ comparison between the blood-pressure in the two arms had been made however

4 Note the ery striking course of the blood-pressure in this patient.

5 This patient lived fifteen years after the recognition of her aneurysm, in good health, life of exceptional though well balanced activity A moderate amount of bismuth and sulpharsphenamine in the earlier years was followed by annual courses of iodid. Only in the last year of her life did even slight signs of cardiac failure ppear She died suddenly age seventy-three cause not identified. Her blood pressure for a decade had been 220/115.

Fig. 718.

THE CLINICAL PICTURE OF SUBCLAVIAN ANEURYSM

This sketch is a composite of 2 almost identical cases, but neither completely examined. Both patients were men, and thirty-six and forty-one years respectively. The former is designated as "A," the latter as "B."

Chief Complaint: "B" "muscular rheumatism" left arm and shoulder. "A" pain in chest and "funny feeling" in neck.

"A" pain is brought on by any exertion.

"B" pain is almost constant, or lasts for days, originating at the upper edge of the scapula and running down the arm.

"A" feels as if he had something in his throat all the time. He is very short of breath on exertion.

"B" is less affected.

Physical Examination

"A" has heart out to the axillary line. There is a thrill on both sides of the neck much more marked on the left above the clavicle. There is likewise a bruit at the second left interspace. Pulse said to be equal both sides, but on measuring the blood-pressure it reads: Right 148/63, left 165/83.

"B" no heart measurements. Pulsating prominence, left neck. Dulness upper left chest. Double murmur at all points. Engorgement veins upper chest, shoulder and arms. Slight exophthalmos, left pupil pin-point, but still reacts to light, right normal in size and reaction.

Blood-pressure 125/50.

Blood Wassermann Reaction: "A" positive, "B" negative.

X-Ray of Neck and Chest: "A" none. "B" trachea slightly displaced to right, no apparent cause.

Treatment: "A" did not improve under arsphenamin and mercury—in fact, became weaker and felt worse. "B," on the other hand, became much better and his signs receded to the point where only an aortitis with regurgitation could be recognized two years later. At that time his electrocardiogram showed no signs of myocardial degeneration.

Both Cases Were Diagnosed as Left Subclavian Aneurysm, But "A" From His Symptoms, Had the Spasmodic Pain of Coronary Sclerosis and Other Signs of Myocarditis. "B," on the Other Hand, Had the Steady Aching Pain of Aneurysm and Almost No Evidence of Myocarditis.

"A" failed under treatment, and "B" recovered almost entirely.

Discussion

1. These two cases make a valuable comparison, for between them most of the signs of left subclavian aneurysm appear accompanied in the one case ("A") with the extreme precordial pain and marked dyspnea on exertion which is the symptomatic suggestion of myocardial insufficiency. Note the pulsation, thrill, and bruit in the left cervical and supraclavicular regions, the signs of aortic insufficiency in "B," the pinhead spastic pupil from paralysis of the cervical sympathetic on the left, the unequal blood-pressure in the two arms (not characteristic of the subclavian aneurysm alone however). Note that the x-ray does not disclose the aneurysm, but shows displacement of the trachea. Without the physical signs, substernal goiter might be thought of. Note also that the blood Wassermann reaction in "A" is positive, in "B" negative, though "B" recovered under treatment.

2. The contrast in the reaction to treatment seems to bear out other cases here presented in showing that the outlook in late syphilis of the cardiovascular system, and especially of the heart and aorta, is dependent to no small extent on the condition of the coronaries and the myocardium. If marked signs of myocardial damage, especially long-standing angina pectoris or precordial distress coupled with electrocardiographic signs such as T wave negativity in Leads I, II, or both, and aberrant QRS complexes are present, treatment accomplishes comparatively little except temporary relief of aneurysmal symptoms. If begun too precipitately much damage and even a fatal outcome may be the result. On the other hand, aneurysms seen fairly early with marked mediastinitis but sound myocardium, seem to tolerate treatment much better and achieve often quite striking results.

Moore, Danglade, and Reisinger give a vivid illustration of the critical problem that conjunction of paresis and cardiovascular syphilis may present in the person of patient with cardiovascular syphilis who was brought to the point, by cardiovascular management, at which he could undergo malarial inoculation, only to have the chills stopped as his cardiorenal mechanism began to fail and then, following further careful nursing, to have the malarial siege renewed with ultimate remission of the paresis.

Fig. 719

EARLY DIAGNOSIS OF AORTIC SYPHILIS CONFIRMED BY SUBSEQUENT OBSERVATION. ACCENTUATION OF SIGNS UNDER TREATMENT WITH PROGRESSION OF LESION. IMPORTANCE OF CARDIOVASCULAR STUDY IN THE FIXED POSITIVE BLOOD WASSERMANN CASE

Business man, aged forty-five years, married.

Examined August 21 1919.

Chief Complaint Stomach trouble. Vomiting after meals, emaciation. Five months duration.

N History of Syphilis; several ttacks of gonorrhea. Wif and three children well.

Left Testicle Removed for "Sarcoma year before present examination.

General Examination N gative including -ray of the stomach. Blood-pressure 118/70, heart negative. Achlorhydria.

Blood Wassermann Reaction: Strongly positive, repeatedly

Consultant Note "Stomach and testicle both syphilitic (?)

Treatment: Six injections arsphenamin, 15 mercury succinimid, 35 inunctions.

Spinal Fluid Negative.

Wif 's Blood Wassermann Reaction Strongly positive.

Children Three, one with peripheral choroiditis, Wassermann reaction negative on the blood.

On Return for Observation After Above Treatment, Greatly Improved, But Blood Wassermann Reaction Still Strong Positive

Because of This Blood Finding he was sent for special cardiovascular study by Willius.

Cardiovascular Examination (Willius) No cardiovascular symptoms.

Heart 4 by 9.5 cm. N arhythmia.

Second sound at base accentuated, especially t the aortic area where the sound accentuation is lmost rasping in character This suggests rigidity of the aorta indicative of peri-aortitis. N murmurs heard.

Blood-pressure 130/76. Pulse 60.

-Ray of chest negative.

Electrocardiogram Rate 53, sinus bradycardia, left ventricular preponderance.

Diagnosis Probably early peri-aortitis, syphilitic.

Treatment: Second course of 6 arsphenamin injections, 20 mercury succinimid, 36 inunctions.

Cardiovascular Re-examination: Nine months after the above. No complaints or change in symptoms. Blood-pressure 138/72. *Diagnosis* peri-aortitis.

Blood Wassermann Reaction: Still strongly positive.

Treatment: Third course of 6 injections of arsphenamin, 18 mercury succinimid; 24 injections mercury salicylate at home

Returned After Three Years' Absence Felt in best of health and condition. N complaint

Cardiovascular Re-examination (Willius) N complaints. *Heart dulness* 4 by 10 cm. N arhythmia. *Systolic murmur* t aortic area. *Diastolic blow* also heard with point of maximal intensity to left of midsternum.

Capillary and water-hammer pulse.

Blood-pressure 162/80, pulse 60.

Electrocardiogram: Rate 60 Sinus bradycardia. Inverted P wave III, Inverted T wave III, left ventricular preponderance.

Diagnosis Syphilitic aortitis and aortic regurgitation.

Fig 719 (*Continued*)

DISCUSSION

1 Note that at the time this patient presented himself he showed no sign, and has never made any complaint which would serve to identify the most serious aspect of his medical condition. Note that his wif had positive blood Wassermann reaction. Note that though the children's blood Wassermanns were negative one of them had peripheral chorioiditis.

2. The investigation of the patient' cardiovascular system was inspired by the fact that he had resistant positive blood Wassermann reaction. His chief complaint of stomach trouble, associated in this case with an achlorhydria and not with neurosyphilis, was promptly relieved by treatment.

3. The examination of the cardiovascular system disclosed an accentuated aortic second sound almost rasping in character interpreted as suggestive of rigidity due to peri-aortitis.

4. This cardiovascular examination was made after the patient had been under treatment six months. Does it then represent the progress of lesion not previously detectable, in spite of treatment, or sclerosis of the aorta either as result of involution of peri-aortitis or from the toxic action of the medication?

5 Of these possibilities it seems to me the more probable that we are dealing with sclerosis associated with healing, rather than lesion newly developed in spite of treatment.

6. During subsequent nine months, while the patient was under fficient treatment, the lesion showed no progress.

7 It was not until after three years of practical lapse from treatment, with the intervention of mercurial of low efficiency and cumulative toxic effect, that the process had dvanced to the point where the original diagnosis by Willius was confirmed by incontestable signs.

8. Note the course of the blood-pressure in this patient. At the outset it was 118/70. After six months of treatment had produced presumably some healing sclerosis, 130/78. After second course of treatment, 138/78. After three years absence, with the development of full aortic regurgitation, 160/80. This rise in blood-pressure during the treatment of an early aortic lesion has been apparent in some of our other cases. If the disease is arrested it becomes stationary In this case it progressed.

9 Are we to assume then that this case progressed because of or in spite of treatment? It is impossible to give categoric answer that will make the mechanism luminously clear t this stage of our knowledge. My personal hypothesis is that the lesion progressed in part because treatment was not carried far enough, and paradoxically because it was carried too far The progressive arteriosclerosis which this patient presents was first increased by the rigidity induced by healing fibrosis. The lesion then became stationary for time. But as soon as more intensive treatment was stopped, it resumed its progress. The slow action of mercury hich with an insoluble salt must have been prolonged through good deal of the period of lapse, may have contributed to the sclerosis. W forget too easily that mercury as well as arsphenamin is poison to the vascular system.

10. From the standpoint of the general diagnosis of syphilis note this patient's surgical history and the fate of probable gumma of the testis diagnosed sarcoma."

While such an example represents expert management at its best and while we have already reviewed the Continental opinions as to the relative benignity of cardiovascular syphilis in the presence of neurosyphilis, the treatment decisions and procedure involved certainly require more than ordinary judgment. Wagner-Jauregg maintains that cardiovascular syphilis tolerates pyrexial therapy well and while Jagic and Spengler take the same stand, our limited experience has not been so encouraging. Cardiovascular collapse is a grave risk to invoke if a method which avoids it is available, and the most disconcerting and, one might almost say unpardonable deaths which we have observed under fever therapy have seemed to be chargeable to cardiovascular complications. Tryparsamide therefore at least deserves first consideration

(Moore *et al* were prevented from using it in their case by the presence of optic atrophy) Wile (1941) has apparently found tryparsamide itself "singularly beneficial" in certain cases of early syphilitic aortitis and early aortic dilatation. We have also found the amount of arsenical and heavy metal constituting preparatory treatment in many cases of symptomatic neurosyphilis before pyrexia or tryparsamide, sufficient to improve markedly the cardiovascular lesion and status. It is well to remember in patients with marked cerebral arteriosclerosis, the great uncertainties intrinsically attendant on prognosis and to make no promises as to treatment results.

Arrest *versus* Palliation.—It is to be feared that reaction against the use of intensive treatment and particularly of the arsenicals in the treatment of cardiovascular syphilis will needlessly deprive younger patients with a favorable background of their outlook for complete arrest by an overcautious tendency to use the symptomatic approach essential in cardiac "wrecks. Figure 719 illustrates a situation of this kind which we feel would be duplicated in any extended review of the application of minimal treatment to cardiovascular syphilis. One way to meet the necessity for moderate intensity just as in the case of irregular and desultory treatment in early syphilis, is by prolongation and continuity In the effort to secure lasting results and genuine arrest in cardiovascular syphilis, nothing less than continuous treatment, practically without rest intervals, over a period of years, should be considered. In all such prolongation of treatment, danger of cumulative effects from the use of insoluble salts must be borne in mind and it is this which gives the better-absorbed bismuth preparations and the low-dosage arsphenamines their genuine advantage

In prolongation of treatment also, even with the minimal intensity of mercurial inunctions and iodides, lies the best hope for palliation in the cardiac wreck, so that the decision between an aim for arrest and one for palliation is primarily one of selection of drugs and dosage in the light of the patient's probable tolerance and potential reaction background.

Selection and Technic of Treatment.—While it is a safe general statement that the arsphenamines (except in very small doses or as bismuth arsphenamine sulphonate) should not be used at the outset in cardiovascular syphilis, it is not wise to underestimate the value of the arsphenamine phase in the treatment of cardiovascular syphilis. Reid observed in a series of cases that the life expectancy of patients who had had arsphenamine appeared to be longer than that of those who had had mercury alone. Conybeare in a small but well-controlled series of 23 patients with aneurysm 11 of whom were treated with neoarsphenamine and 12 observed as controls, found that even though the amount of the drug used was small in all but two of the cases (1 to 8 injections) seven were still living and four able to do heavy work over an average of forty months from the onset of symptoms while of the untreated patients, only four were living with an average duration of life of forty-five months and eight were dead in an average period of ten months. Kothny and Müller Deham employed neoarsphenamine intravenously in ascending doses of 0 05 0 1 0 15 0 2 and so forth every five days to a week until from eight to twelve doses had been given. The symptomatic results were satisfactory but no returns in terms of mortality were given. The majority of the systems from which the present consensus has developed combined the neoarsphenamine therapy with heavy metal, usually mercury Thus Schottmüller has advocated in spirited fashion a higher individual and total dosage (0.5 to 0 6

Gm neoarsphenamine) with numerous case reports but no satisfactory mortality statistics. Cotton treated 55 patients most of them with aortic regurgitation, with courses of neoarsphenamine and mercury reserving 55 untreated patients as controls and finding that the mortality in the treated patients was 25 per cent, that in the untreated patients, 34 per cent, over a five-year period. Herrmann and Jamison employed a neoarsphenamine dosage scale similar to the Kothny Müller Deham system with alternating courses of mercury iodide and bismuth totalling three courses of neoarsphenamine of 3 0 Gm. each. Their results, as analyzed by Moore, Danglade, and Reisinger indicate that of 40 patients who received little or no treatment the mortality was 70 per cent while of 58 patients who received a moderate amount of treatment, the mortality was 55 per cent.

The two most serviceable expositions of results produced by combined treatment with neoarsphenamine and a heavy metal now extant are those of Hines and Carr and the frequently cited results of Moore, Danglade, and Reisinger The former employing neoarsphenamine in doses of 0 1 to 0 45 Gm., the second dose being 0.3 Gm the neoarsphenamine injections weekly for eight to twelve weeks, the heavy-metal course weekly for six to eight weeks, the total period of treatment one year when patients could be induced to follow it, led to the following results. Symptomatic improvement due to neoarsphenamine as such, in the opinion of the authors, occurred in 57 per cent of the cases. Twelve per cent showed aggravation of symptoms. Temporary clinical improvement occurred in 72 per cent of simple aortitis, 41 per cent of aneurysm, and 40 per cent of aortitis with regurgitation. Pain and dyspnea and palpitation were relieved or improved in about one half of the cases. Moore, Danglade, and Reisinger studied 105 patients of whom one third (57) died, 13 of other causes than cardiovascular syphilis, using a method of treatment beginning with a bismuth preparation (0 1 Gm.) every four or five days with iodide 1.3 Gm. to 1.4 Gm. three times a day for ten to twelve weeks. If a satisfactory degree of cardiac reserve was established, neoarsphenamine was given intravenously in doses of 0 05 to 0 1 Gm. initial and 0.3 Gm. final dose with a course of 10 to 12 injections. These two types of courses alternate throughout a period of two years continuous treatment. The results achieved were as follows In 57 patients with aortic regurgitation who received little or no treatment, the mortality was 91 per cent as compared with a mortality in the well-treated patients of only 16 per cent. The average duration of life in poorly treated patients was thirty months, in the well treated patients, seventy-one months. In the case of aortic aneurysm, the mortality during the period of observation for poorly treated patients was 90 per cent, for well-treated patients, 40 per cent, and the average duration of life for the poorly treated patients, nineteen months as compared with seventy five months for the well-treated patients.

It should be emphasized that in the principal series here described adequate treatment of the heart from the cardiologic standpoint was carried on in conjunction with the antisyphilitic treatment, both in the test series and the controls.

From the theoretical considerations now familiar to us plus the methods described in these reports, neoarsphenamine has been accepted as the drug of choice. The dosage range lies between an initial dose of 0 05 and 0 1 Gm. with a maximum of 0.3 to 0 45 Gm. The advent of mapharsen is still too recent for its evaluation, but its nonreactive record in itself would seem to recom-

mend it in a condition where treatment reaction has such bad effects. Appel (1937) reports favorably on its use, which is steadily on the increase in clinical practice. The initial dose should not exceed 10 milligrams, the maximum 30 milligrams (Moore, Howles) In rare and exceptionally tolerant instances the dose of 0 06 Gm. may be reached. In all but the earliest and most uncomplicated cases of aortitis it is advisable to use a preparatory course of a heavy metal ranging from six to twelve weeks. If mercury is employed, the succinimide ⅙ grain (0 01 Gm) to ¼ grain (0 016 Gm.) may be given three or four times a week for a series of twenty to thirty injections. If bismuth is employed at the outset, we believe it wisest to give not more than 0 025 Gm. of a preparation averaging 50 to 60 per cent metallic bismuth for the first half dozen injections, using intervals of four to six days. Insoluble bismuth salts should be given at four to seven-day intervals after the average dose of 0 1 to 0.2 Gm of the drug is attained The water-soluble sodium bismuth tartrate twice a week often acts very well at one half the adult maximum dose. Small doses of bismuth (one third to one half adult dose at the maximum) can be given intramuscularly simultaneously with the intravenous arsphenamine to any patient who can tolerate the described dosage of neoarsphenamine alone. It is essential to carry treatment in alternating courses through from eighteen months to two years.

Bismuth Arsphenamine Sulphonate.—The favorable impressions produced by this drug on Stokes, Miller and Beerman, have been confirmed tentatively by Moore, Reinnger and Danglade. It should be given in an unbroken series of from 40 to 80 intramuscular injections, the first 10 of which are at three- to five-day intervals, the later injections five to seven days. The initial dose is 0 025 Gm intramuscularly increasing gradually to 0 1 Gm. in 10 to 20 injections. The remaining injections are increased quickly to the full adult dose of 0.2 Gm., which is then continued throughout the remainder of the series. There seems to be no limit to the tolerance of the drug in all but occasional patients, and the tonic effect is marked.

Beerman, Shaffer and Livingood (1942) in fourteen year follow-up study of the patients in Stokes, Miller and Beerman group as well as 70 additional patients, considered bismarsen as safe and effective drug for patients with cardiovascular syphilis.

Mercury in Cardiovascular Syphilis.—Mercury while it practically never gives rise to significant therapeutic shock effects, does not *ipso facto* constitute adequate treatment for early cardiovascular syphilis in which there is hope for arrest of the disease. Mercury by mouth in particular is only allowable in the late cardiovascular wreck whose myocardial and coronary involvement is such that nothing more effective can be tolerated or as interim rest treatment in patients receiving courses of more intensive treatment. Mercury by inunction is a satisfactory use of the drug either alone or as a preparation for later arsphenamine treatment. Among the disadvantages of mercury in cardiovascular disease must be included a certain amount of depressing and hemolytic effect, especially serious in anemic patients. The bed patient probably gets the best effect from it. Clinicians dealing with the heart too often forget that the inunction is a very slow method of putting a patient under antisyphilitic medication and that it scarcely begins to take effect in less than two or three weeks after it is begun. Accordingly some weeks or even months of inunctions may be needed for an adequate preparation for either bismuth

or the arsphenamines used intensively for curative effect. For this reason, particularly in the decompensated syphilitic heart, the use of a soluble mercurial salt intramuscularly is much more effective than the inunction. The insoluble salts of mercury given intramuscularly have lost ground since the advent of bismuth and need rarely be used.

The Iodides in Cardiovascular Syphilis.—In the treatment of cardiovascular syphilis the iodides deserve a high though in many respects an intangible place. They should be used invariably and from the outset in every case of actual syphilitic vascular disease They should not be used in treatment given as a therapeutic test for syphilis, for their action is too nonspecific. An exception to this rule may be made where the issue is between syphilis and malignancy when iodide may be used to hasten any favorable result on which a decision may depend. For a time we used the sodium salt, believing it less depressing to the heart, but since Osborne showed that the sodium ion is substituted for the potassium as the drug appears in the circulation, we have returned to the use of the potassium salt without observing any notable disadvantage. Stewart and Smith (1941) however have warned of the serious toxicity of potassium for the heart as shown by EKG studies which would seem to interdict large doses. If there is marked idiosyncrasy sodium iodide by mouth is the better tolerated The dosage should range, for prolonged constitutional effect, between 5 and 10 grains (0.33-0.66 Gm.) three times a day Where gastric irritability is a serious issue, the organic preparations siomine and lipoiodine may be used. There are no advantages that we have observed in giving sodium iodide intravenously to cardiovascular patients, and there is risk of overloading the circulation. In the general picture of cardiovascular-renal disease with hypertension, associated with syphilis, iodide is sovereign, and should often be used alone for some time before mercury or arsphenamine is considered. Intravenous sodium iodide appears to have no significant effect on peripheral arteriosclerotic gangrene associated with syphilis.

Technic of Therapeutic Test.—This is essentially identical with that for the treatment of the various types and grades of cardiovascular lesions, for above all no harm should be done in the attempt to reach a diagnosis. If there is a question whether the lesion is streptococcal, rheumatic, or syphilitic, it is conservative to employ only mercury and iodide for a considerable period, for arsphenamine shows definite evidence of some nonspecific effect on streptococcal lesions elsewhere in the body On the other hand, too intensive use of mercury may unfavorably affect a septic type of process. No attempt should be made in such cases to confuse the issue by removal of tonsils, administration of salicylates, and so forth, until the therapeutic test for syphilis has had a reasonable period of trial. This should be a minimum of six to eight weeks, and it should be recalled, too, that some transient exacerbation of symptoms may occupy part of this time. The time schedule of the action of a soluble mercurial salt may be inferred somewhat from Fig. 720 We know of no definite data on the rate of action of soluble bismuth salts (sodium bismuth tartrate, iodobismitol) which would be preferable, with proper caution in dosage, if there is renal embarrassment.

The Prognosis of Cardiovascular Syphilis—Life Expectancy—The improvement in life expectancy under modern methods of treatment has been touched upon in reviewing the advocated methods of procedure. The comparatively dreary outlook of the large proportion of cardiovascular cases without treatment or under ineffective methods may be inferred from the

earlier reports, and the improved prognosis under adequate treatment in the later ones (1933 onward)

Locke and Rea quote several authorities on the duration of life after the clinical recognition of aneurysm as ranging from twelve to thirty months. Reid also emphasized the relatively short duration of the symptoms before the death of the patients in his most recent series, in more than half the cases, less than eight and a half months. He quotes Emerson as finding that death usually follows within two years after the development of disabling symptoms. Scott found that the agreed average duration of life after the onset of symptoms in untreated patients with aortic regurgitation is only from one to two years. The average age of the patient with syphilitic cardiovascular disease at the time of death, according to Willius, ranges from forty-nine to fifty-four years, and the average duration of the disease in his series was from twenty-three to twenty-six years.

More recent figures clearly show increased life expectancy after adequate antisyphilitic treatment in cardiovascular syphilis. Grant (1935) concluded from a comparison of the survival periods in 82 cases treated with neoarsphenamine and mercury with those in 160 treated with iodide or with no antisyphilitic therapy observed for ten years, that specific treatment after discovery of cardiovascular syphilis definitely prolonged life. Over one third of his series survived the 10-year observational period, the death rate being 64 per cent which was no higher than in other forms of heart disease in his collection of 1000 cases. Padget and Moore (1935) in a study of 106 patients with aneurysm divided almost evenly between inadequately and adequately treated, observed for more than one year more than twice as many of the patients who were adequately treated survived this period of observation, and of those that died, their average life duration was nineteen months longer than in the inadequately treated group. This trend was even more apparent among 71 patients with syphilitic aortic regurgitation, also almost evenly divided as to adequate and inadequate treatment, among whom almost three times as many deaths occurred among the inadequately treated group as in the adequately treated patients. Cole and Usilton with colleagues of the CCG (1936) reported that of 102 patients with uncomplicated syphilitic aortitis who were inadequately treated (i. e., received less than 15 arsenical with interim heavy metal injections), 77 per cent were still living with an average duration of fifty-three months since detection of cardiovascular involvement, and 23 per cent were dead after an average life duration of forty-two months Of 165 patients who were adequately treated 89 per cent were still alive after an average duration of sixty-two months, and 11 per cent were dead after an average duration of seventy-seven months. Thus the authors conclude adequate treatment after detection of uncomplicated aortitis not only practically doubled the duration of life but lessened the frequency of cardiovascular syphilis as a cause of death. (7.9 per cent of deaths were considered to be due to the vascular lesion in the inadequately treated cases as compared with 2.4 per cent in the adequately treated group) Of 191 cases of aortic regurgitation observed for one year or longer the survival period was based on the totals in living and dead In the inadequately treated it was forty months and in the adequately treated fifty-five months, the authors concluded that adequate specific treatment of aortic regurgitation definitely prolongs life. In 59 cases of aneurysm observed for more than a year the average duration of life after detection of the lesion was thirty-seven months under inadequate treatment but seventy-five months under adequate therapy

Personally we have been impressed though by only a few cases, with the very good prognosis of simple aortitis with dilatation and aortic aneurysm, when recognized early A long life expectancy is possible where aneurysm is early recognized thoroughly treated at the outset, and not overtreated in the later years. So much depends however on invisible and intangible factors in the physical state of the heart and circulatory system and so much on the ability of the patient to follow an ideal cardiologic regimen, that genuine prognostication is practically impossible

Effect of Decompensation.—The unfavorable effect of breach of compensation on the prognosis of syphilitic cardiovascular disease is, of course, well known At least a part of the more favorable prognosis of aneurysm as compared with aortitis and aortic regurgitation rests here. Moore Danglade and Reisinger found that only 27 per cent of their patients with aneurysm

Fig 780.

DECOMPENSATION IN SYPHILITIC MYOCARDIAL DISEASE, AS INFLUENCED BY TREATMENT FOR SYPHILIS

Housewife, aged forty-two years, complains of loss of control right side, weakness, insomnia, very slow heart.

Examination Very sick patient, broken compensation, thyroid adenomas, mid-diastolic murmur markedly dilated heart, edema of legs and abdominal wall, fluid both bases.

Abstract of Notes. 1

Day 1 Tincture digitalis 8 c.c. by rectum.
2 Slightly better
3 Diagnosis Decompensated Chronic Mitral Endocarditis with Stenosis. Chronic Myocarditis with Auricular Fibrillation.
Digifolin 1 c.c. every three hours, doses.
Worse in afternoon; 800 c.c fluid withdrawn from right chest.
4 Feels better Digifolin 1 c.c. t. i. d. Aspiration left pleural cavity 800 c.c. withdrawn.
5 Still cyanotic. Crepitation right axilla and precordium.
Blood Wassermann Strongly Positive.
More restless. Heart rapid (160) Grating over precordium.
Patient found out of bed.
6 Digifolin 1 c. t. i. d. *hypodermic*.
Syphilologic Consultant Advises No Treatment for Syphilis Until Compensation Restored. Pupils irregular and sluggish.
7 More fluid right base, more distress, orthopnea.
8 Weaker, fluid accumulating Tincture digitalis 2 c.c. t. i. d.
Reconsideration. Antisyphilitic Treatment Begun. KI 10 to 30 gr t. i. d.
Right pleural cavity aspirated, 600 c.c.
9 Mercury Succinimid Intramuscularly ⅛ grain daily

Abstract of Notes. 2

Day 10 Heart fibrillating slowly Right chest filling up again.
Continued in very serious condition.
Vomited. Another course of digifolin.
Liver 4 cm. below costal margin.
11 Weaker could hardly breathe. Orthopnea.
12 Rested More Comfortably
13 Slight Improvement. Still Fluid in Chest, but Patient Could Lie Prone Most of the Time.
14 Looks Better. Fluid higher in chest.
Definitely improved.
15 Edema Decreased. No Edema of Legs, Pulse Volume Good. Patient more comfortable. (Succinimid daily Iodid daily Tincture digitalis 2 c.c. t. i. d. in three-day periods.)
18 Little increase in fluid.
20 General improvement.
21 Bradycardia, heart regular strong, rate 56.
23 Neurologic examination. Paralysis right arm now apparent.
24 Up in chair
27 Fourteen injections mercury succinimid to date. Iodid continuously since eighth day Improvement began third day after succinimid was begun.

DISCUSSION

1 Digitalis and digifolin, rest, morphin, aspiration of chest, and so forth, seem to have failed to produce any response in this patient until after the institution of mercurial therapy The digitalis preparations used were not chance lots and hence possibly worthless, but the stock preparation of a large cardiac service. The improvement began at about the time when the good effects of a soluble salt in a therapeutic test usually appear

2. While a result apparently as clearly traceable as this is unusual the treatment of decompensated syphilitic patients by mercury and iodid, or with bismuth, may well be begun as soon as the syphilis is recognized.

3. It is almost an axiom that syphilis, even though apparently only concomitant, and not causative affects unfavorably almost every type of disease or lesion. To treat it is, therefore, part of the treatment of the primary process, whatever it may be. In this case the valvular lesion was probably not primarily syphilitic.

had previously suffered from congestive failure at the time of admission, while 46 of those with aortic regurgitation had so suffered. They found that the appearance of cardiac failure before treatment is begun, shortens life on the average from six to fifteen months. It is not, however, a necessary barrier to the successful outcome of treatment. The incidence of cardiac failure in patients who had experienced it before treatment was twice as great during or after treatment (82 per cent) as in those who had never sustained a failure (40 per cent). The seriousness of the situation of the large body of patients, especially Negroes, who are under the necessity of earning a bare living by heavy manual labor can be imagined and in all probability Moore's figures read high because of the high proportion of this type of patient in the clientele of the Johns Hopkins Clinic. The outlook in private practice should be materially better.

Restoration to usefulness, take it all in all, and the regaining of the livableness of life mean almost as much as life itself to a proportion of cardiovascular patients. Conybeare, Schottmüller, Stokes, Miller and Beerman, and Moore, Danglade, and Reisinger have observed striking instances of restoration even to full physical working capacity. The last mentioned authors found that of their 56 surviving patients, 21 were symptom-free and still able to work and only 9 were entirely incapacitated. Twenty-eight of the 47 who could still work had been well treated for syphilis.

Relief of Symptoms.—Our experience with bismarsen has been mentioned in connection with that drug and represents optimum results. The results obtained by Hines and Carr with a neoarsphenamine-mercury regimen are mentioned in discussing systems of treatment. Moore *et al.* found the probability of symptomatic relief to be in direct proportion to the amount of treatment given. In aneurysm under inadequate treatment, half the patients obtained relief; under adequate treatment, nine tenths. In aortic regurgitation approximately 30 per cent obtained relief; of well treated patients, 85 per cent.

Special Problems—Management of Decompensation and Congestive Heart Failure.—We have already noted the seriousness of decompensation from the prognostic standpoint in syphilitic cardiovascular disease, and we have noted its greater frequency as described by Moore *et al.* in untreated and poorly treated cases, in comparison with those effectively treated. We have also pointed out the desirability of coincident treatment with a mercurial for the syphilis which underlies breach of compensation in a previously untreated patient. The first step in the control of this complication should be restricted activity and in the more serious cases, complete bed rest during the introductory phase of treatment. We have repeatedly observed, particularly in those cases which have reached the border line between simple aortitis and aortic regurgitation, that with anything approaching an attempt to push treatment for arrest, the patient passes through a phase of several weeks duration in which there may be slight edema of the ankles, slight dyspnea, definite increase in the size of the heart, accompanying the symptomatic Herxheimer-like increase of precordial stress. This obvious cardiac embarrassment is the probable forerunner of those instances of breach of compensation after treatment is started which have been observed by a number of authors and which rest, restricted activity and intelligent digitalization in the earliest stages of treatment might prevent. The edema and dyspnea particularly respond almost at once to small doses of the tincture of digitalis.

In therapeutic tests of early lesions in which rest might produce a false

improvement in symptoms with subsequent relapse, due allowances may have to be made, but in the later cases it is safer to conduct the therapeutic test under some restriction of activity even if the results are less promptly distinguishable.

Total Thyroidectomy in Angina Pectoris and Congestive Heart Failure.—Blumgart, Riseman, Davis and Berlin have undertaken with apparent success the total ablation of the thyroid as a last resort in congestive heart failure and angina pectoris. This procedure, carried out in 10 cases, acts through reduction of the basal metabolic rate. Beam's report (1941) and Parsons and Purks (1942) shows current experience to support its use in angina rather than heart failure. Long term follow-up at the University of Pennsylvania Hospital (Rose) is favorable.

Digitalization.—When congestive heart failure actually occurs, several observers, including Brooks, Carter and Baker and Moore, Danglade and Reisinger have observed that cardiovascular syphilis, especially in Negroes, seems to be more refractory to digitalis than other forms of cardiac failure. The last mentioned authors recommend the use of powdered digitalis in a dosage of from 0.1 to 0.2 Gm. daily even for use in ambulant patients with a low cardiac reserve over long periods of time. Carter and Baker have found patients refractory to doses of 0.4 to 0.6 Gm. up to a total of 4 or 5 Gm. In the patient (Fig. 720) illustrating the therapeutic effect of mercury in decompensation, there was no response to digitalis until antisyphilitic treatment was begun. Willius (1942) cautions against the routine or indiscriminate use of digitalis in coronary disease.

Diuresis in Syphilitic Cardiovascular and Hepatic Disease.—The newer mercurial diuretics, mercupurin, salyrgan (mersalyl) and novasurol (merbaphen) have proved quite effective in anasarca from cardiac decompensation and in ascites. Levitt and Levy (1940) rate them as more valuable than digitalis in syphilitic heart failure. Evidence of toxic reaction to them and even death is reported and summarized by De Graff and Nadler, Brown *et al.* and others in J.A.M.A. 119: 998–1011, 1942.

Rowntree, Keith and Barrier secured excellent diuresis in 19 of 20 cases of ascites due to portal cirrhosis, syphilitic cirrhosis and Banti's disease by the use of novasurol, and pointed out that better results were obtained if ammonium chloride was used in conjunction with it. Tarr and Jacobson reported only two instances of mild stomatitis and one of wrist drop in 8000 injections of salyrgan and believe that it is quite as effective as novasurol and much less toxic. Grossmann in 10,000 injections, could recall no damage from salyrgan and was able to continue the use of the drug for months at a time. Wiseman found salyrgan particularly effective, and productive of an enormous diuresis (4 to 6 quarts) in a woman with cardiac edema who received 270 injections over a period of five years. Novasurol was used at the outset. The dose of salyrgan, at first 2 cc., was increased to 4 cc. At autopsy no evidence of injury to the kidneys was detectable.

Nervous Strain and Cardiac Neurosis.—Rest and restricted activities mean more than lessened physical labor although rest from physical work is, of course, important. Business worry, the strain of the thought of syphilis, anxiety about the family and the expense of treatment, must be promptly dealt with and reduced to the lowest possible terms by the therapist. One is called on, moreover, in cardiovascular disease, as we see it, to deal with a definite neurosis, dependent on knowledge that something ails the heart, the center of existence. We have been able to present two patients with very similar lesions simultaneously in our clinic, one of them robust, smiling, and care-

Fig. 781.

SYPHILIS OVERLOOKED IN FIRST EXAMINATION. NEUROSYPHILIS LATER DEMANDED ATTENTION. MYOCARDIAL DISEASE (ARBORIZATION BLOCK AND AURICULAR FIBRILLATION) SUBSEQUENTLY RECOGNIZED. UNEXPECTEDLY LONG LIFE WITH SERIOUS LESION

Railroad man, aged fifty years, single.

First Examined 9/1/1913.

Chief Complaint: Hernia.

At the Time of This Examination Absent Knee-jerks Were Noted.

The examiner curiosity carried him no further. Not even Wassermann test was taken. The patient was operated on with good result.

There was note of gonorrhea, but no mention of syphilis.

Four Years Later Patient Returned. He was having difficulty in walking down the aisle. Slight diplopia.

H Gave a History of Chancre thirty-three years before, with one year of treatment by mouth.

Blood Wassermann Reaction Strongly positive.

Neurologic Examination Knee-jerks reduced, otherwise negative.

Treatment: Six injections of neo-arsphenamin. No mercury

Excellent Response to Treatment: Blood Wassermann reaction negative since. Spinal fluid some months later negative.

No Note of Any Cardiac Abnormality Placed on mercury with chalk and iodid.

Two Years Later First adequate general examination.

Heart 4.5 by 11 cm. Blood-pressure 150/70.

Total Arhythmia.

Aortic roughening.

Electrocardiogram Rat 150, auricular fibrillation, arborization block.

Left ventricular hypertrophy

"Prognosis not good.

This Discovery was Almost Accidental. The patient was sent for general ex- amination as routine, and had no complaint to suggest the necessity for it.

Two Years Later: No cardiovascular complaints. No signs of revival of tabes. Had been taking 2 gr mercury with chalk three times daily intervals. In excellent health, able to do full work.

Heart 8.5 by 10.5 cm.

x Ray of chest. Heart enlarged, some aortic dilatation.

Electrocardiogram Rate 150, auricular fibrillation, slurred QRS all leads. Left ventricular preponderance.

One Year Later: Some puffiness and shortness of breath. Signs essentially the same except for:

Heart 6 by 14 cm. (chest ray)

Aberrant QRS complexes all leads. Auricular fibrillation.

No Treatment for Syphilis. Good response to digitalis. Seen fourteen months later, active and carrying on his usual ork without embarrassment. Several normal bloods and spinal fluid examinations in past four years.

DISCUSSION

1 There is nothing specific about myocardial lesion that clinically proves its syphilitic character The association of myocarditis with clinical syphilis creates presumption of but does not demonstrate, cause and effect. On the other hand, this presumption is strong, and is supported by necropsy and microscopic evidence. Aortic roughening and dilatation here add to the force of the presumption of syphilis as the underlying cause. There are no specific electrocardiographic signs of syphilis of the heart.

2. A therapeutic test on myocardial lesion may show positive results early but later it is likely to be obscured by the irremediable effects of degenerations which leave no outlook for ultimate recovery This is apparently the case here.

3. This patient points th moral that an electrocardiographic death warrant may still be subject to stay of execution if compensation can be maintained.

4 Digitalis (tincture—Upsher Smith) 15 drops three times daily for few days, helped this patient ver his first tight place.

5 From th standpoint of the clinical diagnosis of syphilis, this patient illustrates th following points

( ) The worthlessness of year of treatment by mouth, for cure

(b) The low inde of suspicion of an examiner who noted absent knee-jerks and did nothing about them

(c) It was from cases like this, in which w acted therapeutically on the presenting syphilologic aspect (this se tabes) verlooking some other and more serious aspect of the disease, that we learned the necessity of complete ppraisal of the patient t the outset, if one is properly t comprehend and manage syphilis.

(d) It is conceivable that the short but vigorous arsphenamin course hich this patient received precipitated or accentuated the myocardial damage. It is also possible that the sign now present are the residua of healing fibrosis in the coronaries and myocardium, and that he may live years if he stays within his compensation limit

free the other palpitant, trembling, pale, and ill with fear The most determined and authoritative reassurance is a positive therapeutic asset in these cases, and one is justified at times, at least when talking to the patient, in going well beyond the reasoned limits of the prognosis. The real outlook may be disclosed to a trusted member of the family It is the sudden assumption of an overload, physical or mental, which must be impressed on these patients as being the chief menace to their safety If they remain within bounds, they may as in Fig 721 astonish the prognosticators by their ability to survive their myocardial death warrants.

Sedatives and Occupational Therapy —Certain patients with cardiovascular syphilis do not react well to sufficient rest in bed, and must have more liberty of movement. This difficulty in hospitalization, however has been greatly reduced by the advent of occupational therapy which patients speak of in the highest terms as a life-saver The bromides, formerly so useful in the treatment of nearly all cases, have been largely replaced by the improvement of the barbital derivatives yet they are still helpful if not too depressant. Quinidine 3 grains twice or three times a day for a day before and a day after an arsenical, is occasionally useful and was proclaimed by one of our patients as a godsend in dealing with his tachycardia. Willius (1942) cautions against its routine use in arrhythmias when coronary disease is present.

Diet.—Restriction of fluids and in general a moderate reduction in the entire diet to prevent gains in weight will be necessary respectively in the edematous and in obese patients. Caution must be used, however in attempting too vigorous reduction. For patients who are annoyed by distention after meals, small amounts of food at more frequent intervals are advised, and Hoffmann s anodyne or peppermint may assist in relieving the gaseous eructation It should not be too readily assumed that all the gastric complaints of a patient with cardiac disease are due to the heart and not to the stomach, and roentgen-ray examination, though not a test meal, should be given to those who are not relieved soon after treatment is begun, provided their cardiac condition permits. There is definite danger in passing a stomach tube in patients with advanced myocardial damage or coronary sclerosis.

Amyl Nitrite, Etc.—Amyl nitrite and nitroglycerin, while valuable for symptomatic relief conceal the favorable or unfavorable progress of angina pectoris and should not be recommended for patients who are being studied for therapeutic outlook. As with the too frequent use of digitalis, they also encourage the patient to overestimate his reserve. The xanthine drugs, aminophylline and theocalcine as vasodilators (LeRoy 1941) are gaining popularity and are demonstrably more effective, though Willius (1942) rates their usefulness by mouth as controversial. He cites the dramatic virtues of the ounce of whiskey when ¼ grain morphine has failed.

Spinal Fluid Examination.—Whenever it has not been carried out as part of the diagnostic study of the case a spinal fluid examination should be made early in the treatment of all patients with cardiovascular lesions, whose age or grave condition does not contraindicate it. This measure is essential in decisions concerning treatment. A patient with an active, even though symptomatic, neurosyphilis, and a well-marked vascular lesion, is definitely restricted in having his neurosyphilis treated by the limitations set by his vascular lesion. He will almost certainly need tryparsamide, and thus should be arranged for from the start. The spinal fluid examination, even if normal on the first occasion, should be repeated at least once during the first year or

eighteen months observation, to be sure that nothing has been lighted up in the nervous system which was previously quiescent.

Focal Infections.—On the general ground that infective foci may be responsible for cardiovascular disease, that they may reduce the tolerance of the patient for treatment and react unfavorably on syphilis in general, we have made it a practice, while our patients are at rest, to remove definitely infected teeth and tonsils if compensation is not endangered thereby. Too strenuous dentistry including the removal of impactions merely because they are potential foci, should not, however be practiced in these cases.

Occupational Disability and Insurance Readjustment.—The existence of disability clauses in many insurance policies now in force may make necessary the certification of patients for total and permanent disability. In the case of large aneurysms in patients with pronounced angina pectoris and marked myocardial damage as evidenced by the electrocardiogram disability from necessary restriction of activity may well be total. On the other hand, the physician should not be dragooned by the pressure of friends and of the patient himself into certifying total disability where it is obvious that such does not exist. The management of some of the problems of cardiac neurosis, to say nothing of outright malingering in this connection, may require the utmost tact, some firmness, and reinforcement by cardiological consultation.

Special Treatment Methods—Control of Pain.—Material advances have been made in recent years in the use of various methods of nerve block and resection for the relief of the pain of aneurysm of aortic disease and angina pectoris.

The more recent reports deal chiefly with paravertebral sympathetic block with alcohol (Levy and Moore 1941) section of posterior roots (Haven and King 1942), severing of preganglionic fibers (Raney 1939) The results are 50–60

Aneurysm under proper conditions of treatment, rest and control of the patient should rarely require other than general antisyphilitic treatment. The treatment of peripheral aneurysms in accessible vessels is surgical.

The wiring operations for the induction of intravascular clotting (Hare 1927 for example have had limited application and decline in use, with recent more encouraging reports based on important technical modifications in wire insulation, current and temperature control, mode of introduction (see Blakemore and King, J.A.M.A., 1938) Johnson quotes Colt indications: aneurysm saccular not fusiform general favorable physical status of patient; failure of response to rest, etc., with rapid progression, aneurysm should have reached and involved chest all.

Cardiovascular Involvement in Congenital Syphilis.—This subject is presented in Chapter XXI (Congenital Syphilis)

CHAPTER XX

LATE SYPHILIS OF THE NERVOUS SYSTEM

Late syphilis of the nervous system is the business and responsibility of the general practitioner While certain aspects of its diagnosis and treatment may demand the help of a specialist, its earliest detection and its effective treatment by an intensive systemic therapy must be in the hands of the average patient's home physician. If he will perform his whole duty by the first two or three years of a syphilitic infection, there will be a reduction of five sixths in the incidence of consequences in the nervous system.

Late syphilis of the nervous system, long regarded as untreatable except by palliative measures, is yielding so rapidly to improved methods of diagnosis and treatment that it is not too much to say that it also can be mastered from the practical standpoint by any reasonably equipped and interested practitioner The spinal fluid examination alone has placed practical though not minute diagnosis on a plane of accuracy undreamed of two decades ago. This chapter is intended to meet the needs of the average well-informed student and practitioner

The Pathology of Late Neurosyphilis.—The most modern conceptions of neurosyphilis attempt to deal with the pathologic changes on the basis of parenchymatous, meningeal, and vascular processes. The older conception of parasyphilis and metasyphilis has lost much of its importance since Noguchi and Moore demonstration of direct spirochetal etiology in 1913. It is still matter for question as to whether processes such as tabes and general paresis are actual syphilids of the nervous system or whether they should be classified as primary or secondary direct or indirect toxic degeneration phenomena. This question is debatable largely on theoretic grounds, and the steady progress which is being made in successful treatment, especially in general paresis, compels an almost daily revision of viewpoint. The term "interstitial" as distinguished from parenchymatous neurosyphilis refers to the embryogenesis of the involved tissues. Mesodermal or interstitial neurosyphilis involves the vessels, membranes, and supportive (glial) tissues, while parenchymatous syphilis involves the nerve cells as such. Nonne's more detailed classification describes four processes interwoven through three groups of structures. These are syphilitic neoplasia or gummatous infiltration; chronic hyperplastic or fibrotic inflammation; vascular changes including thrombosis, obliteration, and miliary aneurysm with hemorrhage and finally primary parenchymatous degeneration. This classification, very satisfactory for pathologic study does not dovetail with the clinical vernacular at present in use. Shaffer and Stokes attempted to combine the two types in practical classification of symptomatic neurosyphilis shown in Fig 788.

While this rearrangement lacks much of being satisfactory it gives the clinician some clue as to the whereabouts of the process and the pathologic equivalents in the conditions with which he deals. Simple meningitis is the earliest detectable symptom and sign-producing aspect of neurosyphilis. Vascular changes are close successors and may like the meningeal changes, begin to give rise to symptoms within few months after the onset of the infection. Meningeal syphilitic processes localize first at the base of the brain and secondly at the convexity The vascular processes, while frequently affecting the circle of Willis, may involve the finer capillary circulation primarily Acute and chronic syphilitic basilar meningitis therefore colors most of the symptomatic pictures in syphilis of the brain, giving rise to lesions in the chiasm, the interpeduncular space, and the Sylvian fissure. The involvement of N II, III, IV and VI, and lesions in the seventh and eighth cranial nerves are therefore highly suggestive guides in the diagnosis of late as well as early neurosyphilis Gummatous changes in the pituitary body occasionally occur and diffuse plaquelike or tumor-forming gummatous changes in the meninges are common. The dura is most frequently involved, the arachnoid next, and combinations of gumma and fibrous hyper-

plasia may affect all three layers of the meninges at once. Caseation and softening in gummatous tissue occur precisely as elsewhere in the body. The vascular changes of neurosyphilis are not pathognomonic of the disease. Even the obliterative endarteritis can be simulated in tuberculosis and neoplasia. Perivascular plasma and round-cell infiltration (coat-sleeve type) is, however, one of the chief histologic clues in neurosyphilis. Atherosclerotic changes are frequent in the background of vascular neurosyphilis and are not to be clearly differentiated (Nonne) on histologic grounds from those of other infections and intoxications. Vascular neurosyphilis may give rise, then, t atrophy softening, and degenerative change through injury to large vessel at a comparatively distant point, to the slow degenerative results of chronic inflammation with capillary obliteration and to the comparatively sudden effects of leakage or hemorrhage from damaged vessel wall. Parenchymatous degenerations, while occasionally primary as in disseminated syphilitic encephalitis (Barrett), are more frequently as in tabes and paresis, thought of as secondary in origin. Many observers, however still contend that degenerative changes in these conditions are primary rather than secondary

The accepted classification groups are not self-contained and mutually exclusive. Within the same general clinical picture may be grouped varying proportions of vascular meningeal, and parenchymatous change. This overlapping and interchangeability may sometimes make it extremely difficult to differentiate, for example, paresis from cerebrospinal syphilis. A single symptom such as phasia may t postmortem be found to result from hemorrhage from old organized exudate in local meningitic lesion, or from deeper obliterative change in the arterial blood supply with secondary softening. The difficulty of reconciling serological with clinical pathologic findings, at first very pronounced, is becoming clearer as experience shows the mean-

Fig 728.

A CLASSIFICATION OF NEUROSYPHILIS

Preponderantly meningeal
  Early symptomatic and asymptomatic neurosyphilis.
Meningeal (late) and meningo-vasculo-parenchymatous:
  Cerebrospinal syphilis.
Preponderantly vascular neurosyphilis:
  Hemiplegia, arteriosclerosis.
Preponderantly parenchymatous and parenchymato-meningo-vascular:
  Tabes dorsalis.
  Paresis also paresi (symptomatic latent preparetic neurosyphilis).
  General paralysis

ing of the individual serological items and combinations. There is still, however a large margin of uncertainty in which localized meningitic lesions may accompany general negative serological picture and high-grade degeneration appear and progress without apparent change in the spinal fluid.

Immunology of Lat Neurosyphilis.—The two questions of paramount importance at the present day are those of neurotropic strains of infection and of induced neurotropism through the use of arsphenamines in treatment. The work of Nichols and Hough Levaditi and Marie, and other observers on spirochetal neurotropism has been referred to. Schlossberger and Haines and Severac have artificially induced neurotropism by passing *Spirochaeta pallida* through the brains of mice. Georgi and Prausnitz have found biochemical changes t occur in stock cultures of *Spirochaeta pallida* grown in contact with brain tissue. Plaut and Mulzer have not been able to confirm the claim of an intrinsically neurotropic type of organism, but believe that they have produced such type by ineffective arsphenamine treatment of rabbit syphilis. Some of the strongest evidence comes from the clinical side although it must be conceded that much of it is, like the experimental, contradictory

The entire question is admirably reviewed by Jahnel in the Jadassohn *Handbuch* and by Hutton (1941)

The rarity of somatic syphilitic lesions in patients with neurosyphilis favors the neurotropic strain theory and when such lesions coexist they may be an expression of the two strains not being incompatible with each other (Hopkins, 1930; Hutton, 1941 cf Shaw 1940.) Strong evidence for neurotropic strain is afforded by study of conjugal infections. (Hutton, 1941.) Nonne in 19 pages of case reports and summaries from the literature among which are illustrations of multiple infections by the same woman (as high as 5—Erb) with neurosyphilitic accidents in all the

cases; syphilis presenting the same type of neurological involvement, *transmitted by one partner* (male or female) to successive marital partners; examples of apparent neurotropism in the involvement of the nervous systems in parent and child. Most famous of the "paretic strain examples is that of Martha X (Morel-Lavallée) whose career as *fille de joie* brought three medical students, chemist, an engineer and her last partner to death or paralysis with various forms of neurosyphilis. The converse relation, in the form of what seems familial predisposition of the host to the incidence of neurosyphilis regardless of the source of the infection, is equally well illustrated. Moore and Keidel, and Moore and Kemp, in successive studies from the Johns Hopkins clinic, found that conjugal neurosyphilis occurred in 37 per cent of the patients whose spouses they were able to examine, and that there was definite predisposition to the appearance of parenchymatous neurosyphilis among the partners of persons with parenchymatous involvement, while no such tendency existed among patients with cerebrospinal neurosyphilis. Marie has reported examples of pluriconjugal neurosyphilis in polygamy Livingood and Beerman (1941) described case of transfusion syphilis in two brothers (one the donor the other the recipient) both of whom developed asymptomatic neurosyphilis.

Additional suggestive support for the theory of neurotropic strain is lent by evidence from congenital infections. Kemp and Poole from study of 20 families, found neurosyphilis eight times as frequent in the parents of congenital neurosyphilitic children as in the parents of children suffering from other types of congenital syphilis. These findings are substantiated by our experience and by that of others. (Grotjahn, 1936; Menninger and Grotjahn, 1936 Curtius and Schlotter, 1934; Dekeyser Longuet and Anglade, 1937; Riser Becq and Coundou, 1936; Sakane, 1939 and de France, 1936).

Induced Neurotropism, Through the Use of Arsenicals.—This subject has already been in part reviewed in discussing the general principles of treatment, neurorecurrence and early syphilis of the nervous system. The gist of the matter is this: there is no convincing evidence that the adequate and effective use of arsenicals predisposes in any way to syphilis of the nervous system. On the other hand, there is abundant evidence that an increase in the incidence of neurosyphilis is predisposed to by *inadequate* use of the arsphenamines although treatment may shorten the incubation period of some forms of neurosyphilis. If our present evaluations are sound, very few observers at the present day particularly on the neurological side, are dealing with neurosyphilis that has been even inadequately treated with the arsphenamines, to say nothing of adequately treated. Guy' review of this question brought him to the conclusion that, in this country at least, the incidence of paresis is stationary or slightly on the decrease and the mortality definitely decreasing, which would not be the case if arsphenamine were stimulating the development of neurosyphilis. The observations of Lauter, Marburg, Mattauschek, and Hyder tended to show that cerebrospinal syphilis was exhibiting an earlier onset than in prearsphenamine years; but again the evidence appears to show that it is the inadequate use of the drug which is responsible, rather than its proper use. Moore study of neurorecurrence showed clearly that this manifestation of neurotropism is confined practically entirely to inadequately treated patients and that its incidence rapidly decreases with increase in the amount of treatment, including arsphenamine. Stoner in survey of representative clinics and institutions in the United States, found that in general there was definite decline in incidence of neurosyphilis in the years 1923 to 1927 as compared with 1917 1922. Weatherby in study of 250 cases, found no evidence that arsphenamine given in the early stages of syphilis predisposes to the development of paresis, but that the complication appears in the undiagnosed, neglected, and inadequately treated patient. He noted tendency to earlier onset of cerebrospinal syphilis which might, however in his opinion have passed unrecognized in inadequately treated patients. The majority of his tabetics, while less obviously neglected than his paretics, had had no previous treatment. O'Leary and Rogin examined the records of 500 cases of neurosyphilis entering the Mayo Clinic, at random, during the years 1919–1929 finding that in 78 per cent of the entire series treatment had not been given for syphilis before the patient came to the clinic; 13 per cent had had desultory treatment without arsenicals; 12 per cent had been inadequately treated with arsphenamine and mercury The severer parenchymatous types of neurosyphilis preponderated in the patients who had not been treated during the early stages of their infection, the milder types in those who had been treated. Approximately 80 per cent of the patients in their series experienced some degree of improvement when placed on treatment for syphilis, including the arsphenamines.

The consensus of European authoritative opinion was collected by the German Dermatological Society in 1928 through questionnaire yielding 120 replies from the foremost experts of Europe. On the basis of their opinion the Society unhesitatingly announced that modern treatment for syphilis, especially with the arsphenamines, when properly used in conjunction with mercury and bismuth, is not responsible for any increase in neurosyphilis; and that neurorecurrence is steadily on the decline. Many later studies, notably that of the Cooperative Clinical

Group, have repeatedly discussed and reemphasized this protective action of antisyphilitic treatment (Dedman and Morgan, 1933 Hall, 1935; Wile, Poth and Barney 1936 Kemp and Menninger 1936 *Strandberg, 1937 Vonderlehr and Usilton, 1939 Harrison, 1940- Bottema, 1940-* Barrett, 1941, and others)

Specific Drug Neurotropism.—This holds an exceedingly small place among the complications of arsphenamine therapy Peripheral neuritis is one of the rarest of arsenical complications. Even injury to the optic nerve has been dismissed by such authorities as Igersheimer and Nonne as insignificant. W consider this particular neurotropism more real objection to the use of arsenicals than the alleged general neurotropism. Indirect injury to the nervous system through vascular accidents as in hemorrhagic encephalitis, the occasional precipitation of hemiplegic attacks in vascular neurosyphilis, increased irritability of the cortex in epilepsy and the nervous hyperirritability of the overtreatment syndrome have been genuine but extremely rare complications in our experience. One occasionally sees also evidence of the unfavorable action of arsphenamine on meningeal lesion independent of the therapeutic shock. The successive exaggeration of symptoms with each arsphenamine injection and the enormous rise in cell count are in both of Stokes s patients inescapably associated with the continued administration of arsphenamine, and recovery followed the transfer to mercury and iodides.

The Incidence, Course and Response of Early Neurosyphilis Under Treatment.—The treatment of early which is of course overwhelmingly asymptomatic neurosyphilis recognized only by examination of the spinal fluid, has been discussed from the preventive standpoint in Chapter XIV (Treatment of Early Syphilis) The incidence of asymptomatic neurosyphilis as reported by various authors depends on the stage at which the spinal fluid is examined. An incidence of slight to marked abnormalities, including slight rise of cell count, appears in 40 to 60 per cent of early cases, declining in the early latent periods to from 20 to 30 per cent. The incidence of neurorecurrence or outright symptomatic flare-up following inadequate treatment is estimated at from 1.5 to 10 per cent, the first figure representing fairly adequate modern clinic treatment, the second the disastrous results of the misuse of arsphenamine in its early days. Moore, from special study of the question, estimates 0.2 per cent as the reasonably expected incidence of neurorecurrence in clinical practice with early syphilis. I an analysis of 81 cases he established the gravity of neurorecurrence from the standpoint of ultimate prognosis in neurosyphilis b finding that 40 per cent developed clinical signs and 4 out of 14 cases progressed in spite of thorough treatment. Paresis was observed in 3 patients following neurorecurrence and the rate of development of serious late neurosyphilis may be greatly hastened by antecedent neurorecurrence. In his excellent study of Johns Hopkins Hospital experience, he showed that of 342 patients, 20 4 per cent still had evidence of asymptomatic neurosyphilis after one or two energetic courses of treatment. Classified on the basis of spinal fluid findings, two groups, one with slight pleocytosis and slight increase in globulin, and the other with marked pleocytosis and negative or mildly positive spinal fluid Wassermann reaction, responded to routine continued or slightly intensified treatment. The third type, presenting strongly positive W ssermann reaction on all concentrations of the spinal fluid and marked increase in globulin and cell count, proved resistant to all but intraspinal and prolonged intensive systemic measures. This third group corresponds essentially to the preparetic type with first-zone colloidal test. Its striking resistance to treatment (double that of the milder types) was clearly show in the Cooperative Clinical studies (p 674) In our discussions of treatment it ha been clearly indicated that this third group is the recruiting ground in early neurosyphilis, of the late neurosyphilitic material of present-day practice.

In Fig 793, representing the experience of the Bonn Clinic under the direction of E. Hoffmann, is strikingly shown the rise in the incidence of neurosyphilis early in the disease simply with lapse of time, its decline after two years, and the striking differences produced by adequate as compared with inadequat treatment for the disease. After two inadequate courses the incidence of neurosyphilis is seven times as great as after two adequate courses and after three adequat courses more than fifty times as great.

The Fate of Patients with Normal and Abnormal Spinal Fluids in Early Syphilis.—Particular interest attaches to the pronouncements on this matter by Paul Ravaut, to whom syphilology owes the introduction of the conception of asymptomatic neurosyphilis recognized by spinal fluid examination. Ravaut, while not presenting exact statistical evaluation cites numerous cases to illustrate the following principles. Among patients studied in the early stages of syphilis who presented abnormal spinal fluids, three great evolution-

ary groups appear as follows (1) Patients with spinal fluid abnormalities which persist without clinical signs, completely latent for various periods of time and vanishing without complications (2) patients presenting coincidently both abnormal fluids and slight clinical signs, both of which disappear completely without unfavorable progression in variable lengths of time (3) patients exhibiting progression of both symptoms, signs, and spinal fluid changes throughout a period of years until some clearly characterized neurosyphilitic syndrome appears.

By far the larger part of spinal fluid abnormalities (86 per cent) in Ravaut opinion disappear at the close of the septicemic stage of early syphilis and do not reappear Of the remainder presenting all grades of abnormality from slight to severe, an unnamed and unpredictable proportion may return completely to normal, as evidenced by his observations extending over twenty years. A second group develops trifling clinical signs of neurosyphilis, and thereupon heals as ef-

Fig 722.

THE BONN (E. HOFFMANN) CLINIC FIGURES ON SPINAL FLUID CHANGES IN TREATED AND UNTREATED EARLY AND LATER SYPHILIS (880 CASES)

(After Zurhelle and Kroebel, 1927)

Percent abnormal fluids in cases.

Type of syphilis.	Untreated. Duration under 4 months.	Untreated. Duration over 4 months.	Treated. Adequate courses. 1	Treated. Adequate courses. 2	Treated. Adequate courses. 3	Treated. Inadequate courses. 1	Treated. Inadequate courses. 2	Treated. Inadequate courses. 3
Early (under 2 years)	16	47 8	23 0	7 3	0	48 4	50 0	53 3
Later ("old") (over 2 years)		85 3	50 0	14 3	0	30 1	78 5	56 0

Adequate course includes 12 injections of neoarsphenamine 0.6 Gm. (men) with 12 simultaneous injections of bismuth salicylate, intervals of three to four days between the combined treatments.

fectively as the first group. The third group, after preclinical period of marked or intense abnormality leads to definite and grave neurosyphilis. A fourth group whose existence was contested by Sicard throughout his lifetime, includes those patients with pronounced abnormal reactions of the spinal fluid, including strong positive Wassermann reactions, who never throughout their lives develop any signs whatever of neurosyphilis. Sicard contended that no such group exists, but Ravaut cites number of case examples.

Outcome of the Negative Spinal Fluid.—Ravaut contends that it is impossible to predict which of the various roads above described given case of neurosyphilis will follow His study of the patient who has negative spinal fluid at the outset of his infection leads him to the following conclusions. There are undoubtedly patients who never at any time in the course of their syphilitic infection have an abnormal spinal fluid. None the less, the large majority even of such negative cases pass through what Ravaut calls the period of instability in which the fluid may become slightly positive, either spontaneously or under the provocative influence of treatment and particularly of injudicious or overstrenuous treatment with the arsphenamines. At the end of this unstable period of one or two years the case takes definite turn either toward stability and normality of the meningovascular tissues or toward the development of definite pathologic characteristics. He distinguishes in his prognostic estimate of the significance of the negative spinal fluid, two groups of patients, one which has been continuously negative without ever exhibiting the slightest trace of abnormality and the other which has for time been abnormal even though

Group, have repeatedly discussed and reemphasized this protective action of antisyphilitic treatment (Dedman and Morgan, 1933 Hall, 1935 Wile, Poth and Barney 1935 Kemp and Menninger, 1936 Strandberg, 1937; Vonderlehr and Usilton, 1939 Harrison, 1940; Bottema, 1940 Barrett, 1941 and others)

Specific Drug Neurotropism.—This holds an exceedingly small place among the complications of arsphenamine therapy Peripheral neuritis is one of the rarest of arsenical complications. Even injury to the optic nerve has been dismissed by such authorities as Igersheimer and Nonne as insignificant. We consider this particular neurotropism a more real objection to the use of arsenicals than the alleged general neurotropism. Indirect injury to the nervous system through vascular accidents as in hemorrhagic encephalitis, the occasional precipitation of hemiplegic attacks in vascular neurosyphilis, increased irritability of the cortex in epilepsy and the nervous hyperirritability of the overtreatment syndrome have been genuine but extremely rare complications in our experience. One occasionally sees also evidence of the unfavorable action of arsphenamine on meningeal lesion independent of the therapeutic shock. The successive exaggeration of symptoms with each arsphenamine injection and the enormous rise in cell count were in both of Stokes patients inescapably associated with the continued administration of arsphenamine, and recovery followed the transfer to mercury and iodides.

Th Incidence Course, and Response of Early Neurosyphilis Under Treatment.—The treatment of early which is of course overwhelmingly asymptomatic neurosyphilis recognized only by examination of the spinal fluid, has been discussed from the preventive standpoint in Chapter XIV (Treatment of Early Syphilis) The incidence of asymptomatic neurosyphilis as reported by various authors depends on the stage at which the spinal fluid is examined. An incidence of slight to marked abnormalities, including slight rise of cell count, appears in 40 to 60 per cent of early cases, declining in the early latent periods to from 20 t 30 per cent. The incidence of neurorecurrence or outright symptomatic flare-up following inadequate treatment is estimated at from 1.5 to 10 per cent, the first figure representing fairly adequate modern clinic treatment, the second the disastrous results of the misuse of arsphenamine in its early days Moore, from special study of the question, estimates 0.2 per cent as the reasonably expected incidence of neurorecurrence in clinical practice with early syphilis. In an analysis of 61 cases, he established the gravity of neurorecurrence from the standpoint of ultimate prognosis in neurosyphilis by finding that 40 per cent developed clinical signs and 4 out of 14 cases progressed in spite of thorough treatment. Paresis was observed in 3 patients following neurorecurrence and the rate of development of serious late neurosyphilis may be greatly hastened by antecedent neurorecurrence. In his excellent study of Johns Hopkins Hospital experience, he showed that of 832 patients, 26 4 per cent still had evidence of asymptomatic neurosyphilis after one or two energetic courses of treatment. Classified on the basis of spinal fluid findings, two groups, one with slight pleocytosis and slight increase in globulin, and the other with marked pleocytosis and negative or mildly positive spinal fluid Wassermann reaction, responded to routine continued or slightly intensified treatment. The third type, presenting strongly positive Wassermann reaction on all concentrations of the spinal fluid and marked increase in globulin and cell count, proved resistant t all but intraspinal and prolonged intensive systemic measures This third group corresponds essentially to the preparetic type with first-zone colloidal test whose striking resistance t treatment (double that of the milder types) was clearly shown in the Cooperative Clinical studies (p 674) I our discussions of treatment it has been clearly indicated that this third group is the recruiting ground in early neurosyphilis, of the late neurosyphilitic material of present-day practice.

In Fig 743, representing the experience of the Bonn Clinic under the direction of E. Hoffmann, is strikingly shown the rise in the incidence of neurosyphilis early in the disease simply with lapse of time its decline after tw years, and the striking differences produced by adequate as compared with inadequate treatment for the disease. After two inadequate courses the incidence of neurosyphilis is seven times as great as after two adequate courses and after three inadequat courses more than fifty times as great.

The Fate of Patients with Normal and Abnormal Spinal Fluids in Early Syphilis.—Particular interest attaches to the pronouncements on this matter by Paul Ravaut, to whom syphilology owes the introduction of the conception of asymptomatic neurosyphilis recognized by spinal fluid examination. Ravaut, while not presenting exact statistical evaluation, cites numerous cases to illustrate the following principles. Among patients studied in the early stages of syphilis who presented abnormal spinal fluids, three great evolution-

The grading of spinal fluid according to the degree of involvement is a valuable guide to the treatment and prognosis in asymptomatic neurosyphilis. For patients who have a positive spinal fluid at the time of first examination repeated investigation of the changes in the various tests is essential. It is thus possible to note the tendency of the spinal fluid to improve or to assume more malignant features (trend) Patients with the milder types of positive spinal fluid show serologic reversal to negative following comparatively small amounts of treatment. (The types of cerebrospinal fluid and their prognostic import have been discussed on p 120.) It is the only type of neurosyphilis in which it is possible to appraise readily the results of different systems of treatment, and the effect of the various schemes of treatment gives a good clue to the status of the patient's mechanism of defense against the disease.

Incidence.—The Negro has lower incidence of asymptomatic neurosyphilis than either the white male or white female. Among patients whose syphilis was inaugurated by an extragenital chancre the incidence of asymptomatic neurosyphilis was 11.7 per cent in the cases in which the chancre was located above the neck, and 6 6 per cent in those in which the extragenital chancre was below the neck.

Duration of Infection.—The incidence of asymptomatic neurosyphilis tends to decrease as the duration of the infection increases, while the symptomatic form of the disease increases up to the twentieth year as far as the patients could be followed. The earlier in the course of the disease that treatment is started, the lower the incidence of clinical neurosyphilis.

The Scheme and Amount of Treatment.—The scheme and amount of treatment administered during the early stage of syphilis are potent factors in the prevention of asymptomatic neurosyphilis. Adequate treatment given by the continuous system resulted in the lowest incidence (11.7 per cent) Further evidence is offered that the modern treatment of syphilis does not predispose to the development of asymptomatic neurosyphilis. In 60.5 per cent of the cases in which patients did not receive any treatment for acute syphilis the examination of spinal fluid was found to be positive.

Blood Tests.—The Cooperative Clinical Group study was based on the older serologic technics, since the flocculation tests were not employed during the time these patients were under treatment. The blood Wassermann was negative in 30 0 per cent of the cases in which patients with early syphilis had been treated at the time the spinal fluid as first found to be positive, while of those with asymptomatic neurosyphilis detected during the late stage of syphilis, 22 per cent had negative blood Wassermann tests. A negative blood Wassermann in treated patient does not, therefore, obviate the need for examination of the spinal fluid. Of patients with latent syphilis whose spinal fluid was negative, less than 1 per cent subsequently developed positive spinal fluid. The blood test, either positive or negative, is not guide to the presence of positive spinal fluid in latent syphilis, whereas in early syphilis, the persistently positive blood Wassermann is associated with positive spinal fluid in 74 per cent of the cases. The spinal fluid test was positive in 17.1 per cent of cases in which patients were adequately treated for early syphilis and developed blood Wassermann negativity A blood Wassermann relapse from negative to positive in cases in which treatment has been given is frequently associated with spinal fluid relapse or by an increase in the severity of involvement of the spinal fluid.

Wassermann Fastness.—Wassermann fastness is of more significance in early syphilis than in late syphilis because of the higher incidence of asymptomatic neurosyphilis in the former.

Treatment of Asymptomatic Neurosyphilis.—Treatment by the combined methods as previously described resulted in reversal of the spinal fluid to serologic negativity in 64 4 per cent of 565 cases. In 83 6 per cent of patients with group I spinal fluids and in 44.9 per cent of those with group III spinal fluids treatment produced serologic negativity while for group II type of fluid serologic reversal occurred in 65.3 per cent of the cases. The bulk of these reversals occur by the end of the fifth year of treatment. Of the 565 cases in which the patients were treated by the routine use of arsphenamines and heavy metal alone there was serologic reversal of the spinal fluid in 13.3 per cent at the end of the first year and 26.9 per cent by the end of the tenth year routine

and intraspinal therapy reversed to negative an additional 15.8 per cent by the first and 26 4 per cent by the end of the tenth year routine and tryparsamide treatment increased the reversals by 1.2 per cent the first year and by 5 7 per cent at the tenth year malaria therapy when used after the other types of therapy had failed brought about an additional reversal of the spinal fluid in 2 per cent the first year and 3 9 per cent by the tenth year A few cases in which malaria and all of the other combinations of supplemental therapy were used showed a reversal of the spinal fluid in 1 per cent of cases by the fifth year and 1 6 per cent by the tenth year

Clinical Progression.—In 712 cases in which patients were treated, clinical progression was noted in 2.8 per cent of the early cases and in 7.9 per cent of the late cases. Of the 239 late cases in which patients were adequately treated, 4 6 per cent showed clinical progression, while in 218 in which patients were inadequately treated 11 9 per cent gave evidence of clinical progression. In early syphilis the adequately treated and the inadequately treated patients showed practically the same clinical progression. The prognostic significance of grading the spinal fluid was noted here also in that 2 per cent of those with group I fluids, 6 7 per cent of those with group II and 8.8 per cent of those with group III fluids showed progression to clinical signs of neurosyphilis.

Of these 712 patients 43 (6 per cent) developed clinical forms of neurosyphilis, of whom 12 had dementia paralytica (one previously had progressed to tabes and one to meningovascular syphilis) 10 meningovascular 9 tabes dorsalis, 3 optic atrophy 2 taboparesis, 2 meningeal neurosyphilis, 2 neuroretinitis, 1 neurovascular syphilis, 1 eighth nerve deafness, and 1 neurorelapse. The majority of these progressions appeared by the fifth year of treatment. Of the 364 patients 3 developed clinical signs of neurosyphilis after the spinal fluid had become negative and 14 showed progression in other manifestations of syphilis, such as cardiovascular disease.

The treatment of asymptomatic neurosyphilis may be summarized briefly as follows The patient first should be given the advantage of the simpler routine methods of treatment, especially when the spinal fluid is reported as one of the milder types. If the response is slow that is, if after two courses of treatment improvement in the fluid is not noted, intraspinal or fever therapy should be employed. If the fluid is the paretic type when treatment is started, routine and intraspinal treatment for one or two courses should be used If no material change is noted in the reports of the fluid either the malaria or machine methods of fever therapy are employed, as fever therapy is even more efficient in the prevention of general paresis than in its treatment. Persistence with chemotherapy for several years is sometimes necessary after fever treatment has been instituted, although occasionally the spinal fluid will rapidly become negative after fever therapy and further treatment will not be required. In either event, treatment should be continued until the spinal fluid reverses to and remains normal.

Frequency f Neurosyphilis in Medical Practice.—Most of the estimates of the frequency of neurosyphilis in neurological practice antedate modern serological study and have hence little present-day value Nonne placed the proportion as low as 1.5 per cent in figures based on the years 1903 to 1907 while Grinker estimated that 63 per cent of the organic neurological material in the wards of the Cook County Hospital, Chicago, and approximately 10 per cent of that in private practice, was neurosyphilis.

The frequency of neurosyphilis in general medical practice depends to large extent upon

the thoroughness of the search for signs of neuraxis involvement and the frequency with which the spinal fluid examination is employed. The incidence may be roughly estimated from the diagnostic work of the Mayo Clinic, in which syphilis as whole affects 4 per cent of patients. Repeated surveys have shown that 65 to 75 per cent of the syphilis seen in the Mayo Clinic has neurosyphilitic aspect. Neurosyphilitic patients should, therefore, constitute about 2.5 to 3 per cent of the medical entrants from a rural population. Walker and Haller in 4000 medical patients examined, among whom were 600 persons with syphilis, found 3 per cent of the total number to have neurosyphilis. Grey in small group of 63 nephritics, found 8 patients with unsuspected syphilis, 3 of whom had neurosyphilis as shown by spinal fluid examination. Wender and Sampson found that 17.2 per cent of the admissions to the Corozal Hospital, Canal Zone, during five consecutive years, were suffering from neurosyphilis. Vonderlehr and Usilton (1938) found (Fig. 90) that patients with early syphilis observed ten to twenty years developed 16 9 per cent symptomatic neurosyphilis if untreated, 10.5 per cent if they received less than standard treatment and in 1.6 per cent if they received standard treatment. The probability of developing asymptomatic neurosyphilis under the same circumstances was 6.1 per cent, 5 7 per cent and 1.6 per cent respectively Moore found asymptomatic neurosyphilis to be twice as frequent in the white patients of the Johns Hopkins Hospital as among the colored. Zimmermann states that in late syphilis the difference between colored and white patients consists mainly in the frequency of tabes and paresis, the incidence of cerebrospinal syphilis being the same in both, ith tendency

Fig. 724.

PERCENTAGE OF INSANITY DUE TO SYPHILIS

	Per cent.
Male inmates	6 2
Female inmates.	2 2
Total inmates	3 9
Male admissions	15 5
Female dmissions	6 1
Total admissions.	10 4

The proportion is higher in admissions than inmates because of the short life of patients admitted for insanity due to syphilis.

on the part of the Negro to develop cerebral vascular lesions. If the incidence of syphilis in city hospital population be accepted t the conservative 10 per cent, it may be estimated from the above proportions that 6 to 7 per cent show evidence of neurosyphilis on complete examination. Goldblatt and Vanderem (1939) in study of 1871 Negroes in the Shoemaker Clinic, Cincinnati, upon whom spinal punctures had been made found that the female had less frequent neural and cardiovascular syphilis than the male. They noted greater incidence of asymptomatic neurosyphilis than previously reported, indicating that the percentage of neurosyphilis in the Negro tends more nearly to approximate that in the white race. Eighty per cent of neurosyphilis in the Negro was of the mild type. The incidence of asymptomatic neurosyphilis according to age was shown to parallel that of syphilis; symptomatic neurosyphilis tended to make its greatest appearance about eight years later. Unsuspected abnormality was found in the spinal fluid in an average of 14 per cent of all cases of syphilis, exclusive of those of late active disease in which abnormality of the spinal fluid occurred in 33 per cent. Most of the cases of asymptomatic neurosyphilis occurred during the first five years after contraction of the disease but the majority of the cases of symptomatic neurosyphilis occurred during the eight to fifteen-year period following contraction of the disease.

Frequency of Various Types of Neurosyphilis.—The standard citation in this field is from the group of 4134 syphilitic Austrian Army officers studied by Mattauschek and Pilcz. Of this group, 4.8 per cent developed paresis, 2.7 per cent tabes, and 3.8 per cent cerebrospinal syphilis. The slightly greater frequency of paresis as compared with tabes is borne out by statistical experience in general (Nonne). Pusey quotes Fischer, 2.5 per cent of 1170 syphilitic men and 0.85 per cent of syphilitic women as developing paresis, while 1.6 and 0.32 per cent respectively developed

tabes. Pick and Bandler found 2.1 per cent of syphilitic men developing paresis. The ratio of male to female incidence of paresis determined by Furbush survey for the National Committee for Mental Hygiene is as 6 is to 2.

The incidence of paresis and tabes for the population at large is given by the Metropolitan Life Insurance statistics (as cause of deaths) previously quoted, as ranging downward from 16.0 per 100,000 to 13.1 per 100,000. Kirby gives the hospital admissions for paresis in New York State over a period of years as 8.4 per 100,000. Marie gives the incidence of paresis in Egypt as 5.5 per 100,000

The incidence of the arious types of symptomatic neurosyphilis in the Cooperative Clinical Group material is given in Fig. 725.

Fig. 723

PERCENTAGE OF VARIOUS TYPES OF SYMPTOMATIC NEUROSYPHILIS (COOPERATIVE CLINICAL STUDIES)

Type of Neurosyphilis.	Number	Per cent.
Tabes	985	48.6
Paresis	374	18.5
Taboparesis	149	7.4
Meningeal	177	8.8
Meningovascular	281	13.9
Vascular	108	5.1
Total patients	2,008	100.0

From Kierland, O'Leary and Vandoren, 1942. (Some of the patients had several types of neurosyphilis.)

Fig. 724.

PERCENTAGE OF POSITIVE BLOOD WASSERMANN IN VARIOUS MENTAL DISEASES

	Positive.	Negative.	Total.	Percentage.
Dementia precox and similar paranoids.	3	21	24	12.5
Manic depressive and melancholic states.	11	52	63	17.5
Toxic psychoses.	5	20	25	20.0
Organic and senile dementia.	2	7	9	22.2
Epileptic types	3	9	12	25.0
Pseudogeneral paresis, tabes, arteritis, and local lesions	9	26	35	25.7
Degenerative and constitutional psychoses	14	32	46	30.43
Confusion and acute maniacal delirium	9	11	20	45.0
Total non-paretic	56	178	234	23.9
General paralysis	57	4	61	93.4
	113	182	295	38.3

As a factor in neuropsychiatric work paresis is rated by May the cause of 11 per cent of 70,000 first admissions to 48 hospital in 16 different states. Richards, in White and Jelliffe text (quoted by Southard and Solomon), states that paresis constitutes 5 to 7 per cent of all military cases of mental disease in the French, German, American, and Russian armies.

The proportion of mental disease due to syphilis is summarized from survey covering 84 hospitals in this country by Donaldson, in Fig. 724. Merriman (1935) estimated that neurosyphilis occasioned 11.2 per cent of all admissions to civil stat hospitals during the year end of 1933. In a more recent survey M. Moore and Merritt (1936) found that syphilis is responsible

for the psychosis in 9.3 per cent of 26,157 first admissions of psychotic patients to the Boston Psychopathic Hospital in the first twenty-two years of its existence (1912 to 1934) Fig. 727

Fig. 727

CAUSE OF PSYCHOSIS IN 2,448 SYPHILITIC PATIENTS*

	Patients.	Per cent.
Dementia paralytica	2,231	91 2
Tabetic form of dementia paralytica	66	2 7
Meningovascular neurosyphilis	138	5 6
Undifferentiated neurosyphilis	13	0 5
	2,448	100 0

* 9.3 per cent of 26,457 admissions, Boston Psychopathic Hospital (1912 to 1934) M. Moore and Merritt (J.A.M.A. 107 1292, 1936)

Marie and Levaditi have compiled a table of the incidence of positive blood Wassermann reactions among 295 consecutive admissions for various mental disorders, as shown in Fig. 728.

These figures are definitely too high for American experience with the positive blood Wassermann among the insane which has been summarized as follows

	Per cent.
Sheehan (Government Insane Hospital, Washington)	20
Echols (Georgia State Hospital)	18
Lowrey (Iowa State Hospital)	16

THE GENERAL SYMPTOMATOLOGY OF NEUROSYPHILIS

Clinical literature and case material usually represent signs to be more conspicuous than subjective symptoms. Yet the subjective symptom not infrequently furnishes a valuable early clue to the recognition of the process. Symptoms such as headache, paresthesias, lightning pains are irritation phenomena and accompany the treatable early phases of the disease. Argyll Robertson pupils and lost reflexes show relatively little response to treatment and represent, on the whole, irremediable damage. The preventively-minded observer therefore will develop side by side with his alertness for early signs a high index of suspicion for symptomatology Habitual painstaking complete examination is the only means for the detection of the earliest objective signs. While symptoms and signs in neurosyphilis have a certain localizing value headache, for example, suggesting cortical or basilar meningitis, lost knee jerks accompanying lower cord degeneration seizures, hemiplegias, and aphasias, suggesting cerebral involvement it is more often true that multiplicity wide distribution and shifting character rather than intense localization, suggest a neurosyphilitic process.

Some neurosyphilitic pictures lack specificity and not all neurological symptoms in the course of syphilis are due to syphilis of the nervous system. Particularly effective illustrations can be found in multiple sclerosis, sarcoma, myelitis, glioma, and tuberculous Pott s disease with paraplegia. An examination of the spinal fluid usually but not always clarifies the diagnosis. In some cases a therapeutic test is a final resort, and even here as in multiple sclerosis and glioma, nonspecific therapeutic response makes this procedure of uncertain value.

Such a tabulation as Fig. 728 cannot of course convey the impression of

Fig. 783

AN APPROXIMATE CHRONOLOGY OF NEUROSYPHILITIC SYMPTOMS AND SIGNS

	Symptoms.	Signs.
First to fifth year	Headaches and head pain. Alopecia and leukoderma. Ringing ears and dizziness. Impaired vision. Other symptoms of cranial nerve lesions (diplopia, deafness, facial palsy) Neurasthenoid symptoms: nervousness, lassitude, malaise and pains, phobias, and emotional disturbance. Insomnia. Early hemiplegia and epilepsy	Fixed or relapsing positive blood Wassermann reaction. Spinal fluid findings: Cell count, Wassermann test, etc. Pupillary irregularities, anisocoria, disturbed light and accommodative reflexes. Fundus signs of involved N. II: Papillitis, neuroretinitis, early disk pallor, etc. Disturbed reflexes, usually accentuated. Cranial nerve lesions: Ocular paralyses, facial palsy, low bone conduction, etc.
Fifth to tenth year	Headache and head pain. Stomach trouble. Backache Neuralgias (or root pains) Cerebral neurasthenia: Tremor, fatiguability, irritability, insomnia, memory loss. Seizures and "Spells": Aphasic, epileptiform, apoplectiform, hemiplegic. Paresthesias: Prickling, numbness, burning, tingling	Spinal fluid findings. Pupils, irregular, unequal, or slow Isolated paralyses and pareses. Lower cord reflexes, diminution and loss, or early accentuation and spastic changes. Early sensory changes: Widespread with reduction in pain, bone and muscle-joint sense. Alterations of personality
Tenth to twentieth year	Reduced libido and potentia. Difficulty in urination. Ataxia, noticed first after dark. Failing vision. Diplopia and ptosis. Lightning pains. Girdle sensation and other paresthesias. Visceral crises. Seizures. Mental symptoms. Cardiovascular symptoms.	Argyll Robertson pupils, anisocoria, mydriasis, myosis. Romberg or Babinski and spastic signs. Optic atrophy (primary). Extra-ocular palsies. Lost lower cord reflexes. Hemiplegias and hemipareses. Dysarthria and aphasia. Grandiose and paranoid delusions, conduct slump. Trophic joints and spontaneous fractures. Mal perforans.
Twentieth to fortieth year	Advanced ataxia or paraplegia. Severe paresthesias and pains. Tabetic infected bladder with cystitis. Attacks of fever (pyelitis) Uremic symptoms. Advanced mental deterioration. Arteriosclerotic changes. Apoplexies.	Further progression of the foregoing signs. Rising blood urea and declining renal function.

This summary combines the observations of Fordyce *et al.*, Moore, Lucke, Nonne, Klauder, Riddoch, Kagawa, Mannesheimer, Bolton, Petts, Stokes *et al.*, Gennerich, Leyberg, Nonne, Wile.

the rich and variegated symptomatology which characterizes neurosyphilis as a whole, nor can it make adequate allowance for its restricted specificity But it is a fair representation of the neurosyphilology of ordinary medical practice. The unfolding of the picture may be stopped at any point by the arrest of the disease, or accelerated so that the symptoms of the last decade may furnish the closing episode of the first.

Miscellaneous Clues.—The neurosyphilitic who is up and about presents, in the aggregate, signs three times as often as he does subjective symptoms (Fig 729) The relative importance of various eye signs is shown in Fig 730 Moore, in a survey of 642 early cases, found that of those presenting the symptoms of the first to fifth year (Fig. 728) four times as many (29 per cent)

Fig. 729 (After Stokes and Brehmer—400 cases.)

SUBJECTIVE SYMPTOMS IN PREPONDERANTLY LATE NEUROSYPHILIS

	Per cent.
Gastric symptoms	25
Lightning pains	16
Headache and head pain	15
Diplopia and failing vision	12
Malaise, weakness	10
"Rheumatism"	10
Bladder symptoms (subjective)	[illegible]
Loss of consciousness	9
Girdle pain	8
Ataxia (subjective).	8
Dizziness	8

OBJECTIVE SIGNS IN PREPONDERANTLY LATE NEUROSYPHILIS

	Per cent.
Abnormal knee reflexes	73
Abnormal Achilles reflexes	67
Abnormal spinal fluid	65
Abnormal pupillary reflexes, muscular paralyses, or fundus changes	63
Sensory disturbances	40
Romberg positive	43
Mental symptoms	39
[illegible]	36
[illegible]	35
[illegible]	32
Speech defect	14

had neurosyphilis as among those in whom these symptoms were absent Leyberg found 52 per cent of patients with leukoderma and 60 per cent with alopecia to have involvement of the nervous system (see Chapter XII) Cardiovascular syphilis as an accompaniment of neurosyphilis was found by Nonne in 17 to 24 per cent of paretics and tabetics, chiefly the latter Chiari found 47 per cent; Straub, 82 per cent (postmortem examination) and Fritsch has recently reported 39 per cent in 115 cases (20 per cent in paresis, 48 per cent in tabes, and 35 per cent in cerebrospinal syphilis) Conversely we found (Chapter XIX) 54 per cent neurosyphilis in patients with cardiovascular syphilis, and 40 per cent abnormal spinal fluids. Hopkins, in 1571 patients with clinical neurosyphilis, found 12.9 per cent to present complicating tertiary lesions, 8.1 per cent of the cardiovascular mechanism, 5 per cent of the bones

and 2.4 per cent of the skin. Shaw (1940) showed from a review of the literature and his own experience that all forms of neurosyphilis occurred in from 13 to 32 per cent of patients with mucocutaneous or osseous tertiary syphilis.

The practitioner should then, apply the same objectivity to his diagnosis of neurosyphilis as to any other aspect of the disease. While the patient's subjective complaint may suggest it to him much more often his first clue will be found in the eye signs and the lower cord reflexes, taken as part of a routine physical examination.

Important Symptoms.—A very simple group of tests (see p. 46 and Chapter II) and a brief routine questioning will lead to the detection of a large part of symptomatic neurosyphilis in general medical examination. The overenthusiastic must, however, be cautioned here, as elsewhere, to realize that an isolated symptom does not make a diagnosis, and that convulsions, for example, or papillitis, occur in a variety of neurological conditions, and cannot stand alone as evidence of syphilis. Resort to spinal fluid examination now enables the average physician, discouraged by previous complexities, to reach a diagnosis for his patient in a much larger proportion of cases.

Headache.—This symptom of neurosyphilis may vary from a diffuse moderate, and persistent pain to the severe boring and blinding pain of brain

Fig. 730.

EYE FINDINGS IN NEUROSYPHILIS. (Stokes and Brehmer—186 cases.)

	Per cent.
Total presenting pathologic eye findings	65
Argyll Robertson pupils	33
"Slow" reflexes	23
Irregular pupils	21
Unequal pupils	10
Fundus changes	15
Muscular paralyses	10

tumor with projectile vomiting. It is usually paroxysmal and so severe as completely to unnerve the patient. It may be confused with the pain of osteitis of the skull. The roentgen ray may assist in differentiation.

Extremely severe headache with stiff neck accompanying basilar meningitis has been relatively uncommon in our experience. It is really remarkable what apparently pronounced grades of meningeal involvement of a basilar type may be associated with little subjective distress. Similarly in what are presumably localized meningeal lesions near the chiasm, pronounced objective signs, including high-grade choked disk, may, apart from impairment of vision, be relatively symptomless.

Lightning pains and paresthesias are not only frequent but also extremely early symptoms. The typical lightning pain is sharp, stabbing, spotlike and may recur again and again in the same place, often singling out a spot such as the heel or the instep for repeated shocks. It is most often described as "like electricity" and of agonizing intensity. Of a different type is the deep aching prolonged "bone pain" of tabes.

In other cases, the pains may come in showers over a considerable area, leaving the skin tender to touch for some hours or a day after the shower subsides. There is no aching quality to the pain, no tenderness to pressure, no accentuation with movement as in myositis and myalgia, and no prickling, numbness, or burning as in neuritis. Accentuation with fatigue and unfavorable

weather changes, and with the onset of infections is the rule and probably helps as much as anything to bring about the common diagnostic misinterpretation of rheumatism.

Paresthesias.—These may consist of fleeting attacks of numbness, tingling prickling, constriction, sensations of cold or heat, shifting from point to point or involving an entire limb or side of the body

Fig. 731

UNSUSPECTED ONSET OF NEUROSYPHILIS

Chief Complaint Stricture of the urethra.
History Locomotive engineer gonorrhea fifteen years ago married twelve years, no pregnancies; t time of Neisser infection had two small warty lesions, called chancroid no treatment no secondaries observed.
General Examination Stricture of urethra. *Soft systolic murmur aortic area* (complains of slight dyspnea, no palpitation) Serum Wassermann negative. Because of venereal history referred for special syphilologic investigation.
Syphilologic Examination No genital scar no leukoplakia.
Provocative negative throughout.
Bone conduction Minus 5 *lowered high fork, moderate eighth nerve atrophy*
Eye examination Negative except for *hyperemia of both fundi.*
Cerebrospinal fluid WR negative; Nonne negative; lymphocytes *18* gold sol 1111100000.
Neurologic examination History of lumbago (?) three years ago *pain and burning* (*right leg; heavy feeling in calf prickling in foot, pain in sacral region.* Would not make diagnosis of CNS lesion on findings. Sciatica (?).
Effect of Treatment Advised to begin treatment on above findings. At completion of first course arsphenamin, "Feels 100 per cent. better All symptoms except prickling in foot disappeared. CSF WR negative; Nonne negative; lymphocytes *5* By the end of the second course the prickling in the foot had disappeared. CSF WR negative; Nonne negative; 4 lymphocytes.

They may be highly localized, fixed or slowly extending, as in the ascending numbness of the extremities which we have learned to interpret as an unfavorable sign in patients under treatment. The sensations of cushion feet and of walking on cotton batting are familiar in tabes. Obstinate

Fig. 732.

ONSET OF NEUROSYPHILIS IN PARESTHESIA (?).

Chief Complaint Burning of the skin of neck, fifteen years. Asked to see skin specialist for this. Wife in hospital for operation.
History Locomotive engineer; gonorrhea twenty-seven years ago, no history genital sore or secondaries. Rheumatic pains in right leg fifteen years; left leg two years, left arm now also. Burning in feet began year ago.
General Examination Blood-pressure 140/86, otherwise negative.
Serum Wassermann negative. Diagnosis indeterminate.
Neurologic Examination Slight impairment of hearing to watch tick. Tinnitus left, Romberg, 1 foot, moderate positive. Slightly diminished bone fork and joint sensation. Left Achilles and triceps obtained with difficulty
Eye Examination Negative.
Bone Conduction Not taken.
Cerebrospinal Fluid WR negative; Nonne negative; lymphocytes *32*
Therapeutic Test This was advised on the above indeterminate findings. Spinal fluid taken with the fifth arsphenamin injection showed Wassermann negative Nonne positive lymphocytes 2, and five months later in declining to return for observation, the patient wrote "All the symptoms I came there with have entirely disappeared and I feel you have made permanent cure. Diagnosis still indeterminate.

Itching at given point or burning of the skin may bring the patient to the dermatologist (Fig. 732). Sometimes the patient detects an anesthesia and seeks relief for it, as in the circumanal anesthesia in which the patient cannot feel his stool pass. The girdle sensation of the tabetic, sense as of tight constricting band about the waist or lower thorax, is highly characteristic paresthetic symptom. Disorders of taste and smell may occur but are decidedly rare.

An interesting theoretical discussion of the mechanism of tabetic pain is given by Pochin (1938)

Disturbances of bladder control and of the sexual reflexes are coming into recognition as important early signs of lower cord changes and as among the first warnings of tabetic neurosyphilis in particular The onset of the bladder symptoms may be so insidious that the patient is entirely unaware of the gradually developing atony of the bladder musculature from paralysis due to impairment of its innervation. He believes himself to be emptying the bladder completely when in reality a residual urine of 100 to 500 cc. may be present. The first warning of trouble comes when the patient wets the bed at night from overflow through a contracted sphincter from a distended bladder "Hard to start" is the phrase most patients use to express the difficulty of relaxing the sphincter and emptying the bladder by its own contractility in the earlier irritative phase. "Dribbling" after a supposed complete evacuation indicates either sphincter atony or a retention of urine in an atonic distended bladder The physician has an unmistakable responsibility in detecting these cases, and the repeated catheterization of a patient without an examination of his reflexes and a search for other neurological signs of syphilis is inexcusable. Cystoscopic examination furnishes valuable and usually conclusive evidence of the nature of a bladder retention, but should be resorted to only when actually necessary for diagnosis.

Ockerblad (quoted by Marshall and Carlson) found 30 per cent of tabetics to have disturbances of micturition and 60 per cent to have bladder symptoms. Shaffer' series showed "cord bladder in 43 per cent (Fig. 759). Marshall and Carlson find that the uninfected atonic tabetic bladder has capacity of from 600 to 1,000 cc. without discomfort, as compared with a normal of 300 to 400 cc. Among Emmett and Beare s (1941) series of 977 patients on whom the diagnosis of tabes was made in the Mayo Clinic from 1934 to 1940 there were 419 (42.8 per cent) who complained of symptoms referable to the urinary bladder Rose and Deakin have proposed the measurement of the capacity of the bladder ("cystometry") as method of differentiating the myogenic and prostatic obstructive changes from those of neurosyphilis. The trabeculation of the relaxed atonic bladder is spoken of as neurogenous or "cord bladder which, hile it may occur ith spina bifida and cord tumors, is overwhelmingly more common in tabes than in other neurological conditions. The late infected tabetic bladder may be hypersensitive small and contracted, and the mucosa inflamed and velvety instead of pale and smooth between the trabeculae. It should not be forgotten that a neurogenous bladder and an enlarged prostate may coexist, so that manual examination of the prostate is not substitute for cystoscopy if the neurological signs are equivocal. Attention to neurological signs and spinal fluid examination may do way with the apparent necessity for prostatectomy as pointed out by Dowling.

Cystometry now has had experimental as well clinical evaluation. It is now rated as a technical procedure which may reveal the earliest sign of injury to the cord in neurosyphilis, obtainable before the development of any but minor urinary complaints and even before other objective evidence of neurologic damage can be demonstrated. The interpretation of cystometric abnormalities when neurosyphilis is asymptomatic is as yet difficult since similar abnormalities may occasionally occur in studies of apparently healthy persons (Boyd and Smith, 1938). Cystometry is also of value in differentiating between damage to the posterior columns in the spinal cord as in tabes dorsalis and lesions of the cortico-spinal tracts as in other forms of neurosyphilis. It may also be useful in determining the proper method of treatment, i. e whether one should use acetyl betamethyl choline hydrochloride (mecholyl) as a parasympathetic stimulant or atropine as a parasympathetic depressant, or presacral sympathectomy A complet bibliography of this subject is given in the review by Moore and Mohr (1939)

In the irritative stage of lower cord involvement the patient may as in Fig. 725, present such a symptom as priapism, though this is rare. More commonly there is transient increase in sexual activity usually not recognized as significant, followed by disappearance of potentia and libido, occurring in our series in 23 per cent of cases W have seen Argyll Robertson pupils and loss of potentia the only signs of tabes which had evidently been quiescent for thirty years

The ocular symptoms and signs of neurosyphilis are dependent in the earlier years on meningeal lesions and especially on basilar involvement, al-

Fig. 733.

EARLY LOWER CORD IRRITATION IN CEREBROSPINAL SYPHILIS SIMULATING MULTIPLE SCLEROSIS

Male, aged *forty-seven*, married.

Complaint: Priapism.
Slight difficulty in urinating.

Prostate Negative. Relaxed bladder sphincter some trabeculation, atonic or cord bladder (?)

Neurologic Examination: Pupils slightly sluggish to light. All lower cord reflexes increased. Babinski markedly positive. Midabdominal and anal reflexes absent.

Diagnosis Probably *multiple sclerosis*. "Rule out syphilis.

Syphilologic Examination Negative history one antemarital exposure.

Blood Wassermann Negative.

Eye: Slight blurring of disks.

Spinal Fluid Wassermann negative on 0.2 c.c., positive on 0.4 and 0.5 c.c.; Nonne negative.
Small lymphocytes, 5?
Gold sol, 0144410000.

Treatment Three courses neo-arsphenamin, 16 injections. Mercury succinimid, 2 courses, 20 injections, 100 inunctions in two years.

All symptoms disappeared and patient has been clinically and serologically normal for four years.

COMMENT

An excellent illustration of the clarifying effect of an examination of the spinal fluid in a puzzling case.

Note that the remainder of the examination is frankly negative for syphilis except for the doubtful cord bladder

Excellent therapeutic results, equalling anything in the field of serious medical treatment, can be secured in neurosyphilis by early effective attack, following prompt diagnosis.



Fig. 734.—Slight ptosis and diplopia due to partial paralysis of the third cranial nerve (right) Note the beginning outward and slight downward deviation of the eyeball. The patient recovered under treatment.

though meningitis of the convexity may likewise occasionally give rise to ocular lesions (Nonne) The ptosis, diplopia, and strabismus are parts of the

general group of cranial nerve syndromes (see Chapter XII) and may be slight or pronounced, translent or permanent (Figs. 734–737) Failing vision may be due to primary or secondary changes in the optic nerve While it may ac-



Fig. 735 —Total paralysis of the right third cranial nerve, with complete ptosis, turning of the eyeball outward nd somewhat downward, pupil dilated and immobile, accommodation paralysed, and crossed diplopia. This paralysis was permanent.

company an active inflammatory process, it does not necessarily do so, and vision may be unaffected by a choked disk of several diopters or a marked neuroretinitis. Papilledema of syphilitic origin may occur as a result of basilar



Fig 736.—Right seventh nerve paralysis disclosed by the attempt to smile The eye on the paralysed side cannot be completely closed.

meningitis or optic chiasm arachnoiditis (Alpers and Yaskin 1935) It may occur without increase in intracranial pressure in lesions at the chiasm (Hausman, 1942)

Nonne emphasizes, as do many other authors, that the detection of the real extent of optic nerve involvement cannot be done by clinical signs, but must be accomplished by routine ophthalmoscopic examination and the taking of perimetric fields on *all* patients with syphilis. *Lillie*, in examining a series of Mayo Clinic cases, was impressed with the fact that failure to take visual fields before treatment is begun is responsible for the impression that some drugs cause much damage to the visual tract, when in reality much of the damage is caused by syphilis itself.

Secondary optic atrophy following inflammation or papillary edema is not as significant of grave or extensive neurosyphilis as is the pale gray sharply defined disk of primary optic atrophy. Of the latter Nonne says that practically invariably tabes or paresis is a forerunner or a sequel.

Hausman (1937 1941) made careful studies of the syndrome of syphilitic chiasmal arachnoiditis which may manifest itself as the classic form of primary atrophy of the optic nerve, with heteronymous visual field defects or multiple cranial nerve lesions adjacent to the optic nerve or as the less frequent form of papilledema without internal hydrocephalus or increased intracranial pressure. In differential diagnosis one must rule out an expanding lesion (tumor cyst or aneurysm) which may be intrasellar suprasellar or parasellar arachnoiditis (nonsyphilitic or syphilitic);



Fig. 737.—Bilateral external ophthalmoplegia due to paralysis of the external ocular muscles without involvement of the ciliary body and iris (partial nuclear involvement of the third nerve).

trauma or heredodegeneration. The nature of the pathologic process is such that it compresses the optic nerves and chiasm but it is not known why this local process around the chiasm should produce atrophy of the optic nerve in one case and papilledema in another. Since antisyphilitic therapy offers little relief in these cases, Hausman considers surgery the method of choice. In one of our cases no relief was obtained from both methods of therapy.

The study of the pupillary reflexes as a guide to early neurosyphilis is one in which the personal equation and experience of the examiner plays some part.

The conditions for testing eye reflexes described in Chapter II are not acceptable to some ophthalmologists, who demand a preliminary stay in the dark room and flash testing of the light reflex. If the slightest response of the pupil to light is obtained, it cannot be described as of the *true Argyll Robertson type. Spiller on the other hand, from the neurological standpoint insists* that overemphasis on absolute fixation discourages recognition of early and "abortive" changes.

It is a temptation to insist, for its dogmatic teaching value, that marked irregularity of the pupils, sluggishness, or an outright loss of light reflex, with preservation of accommodation is pathognomonic of neurosyphilis. Nonne, in an excellent review of this question in the light both of the literature and

his experience, concludes that, in the main, reflex fixation of the pupil to light with reaction to accommodation is regarded as distinctive of neurosyphilis in the overwhelming proportion of cases. Adie has defined the Argyll Robertson pupils as small pupils, constant in size, unaltered by light or shade, contracting promptly and fully on convergence, dilating promptly again when the effort to converge is relaxed and dilating slowly and imperfectly to mydriatics.

The value of pupillary signs in the diagnosis of neurosyphilis must be critically considered in the light of our growing comprehension of arteriosclerotic phenomena of lethargic encephalitis and of Adie syndrome. Nonne states that the pupillary disturbances of arteriosclerosis are not typical, but that chronic alcoholism, delirium tremens, the onset of syringomyelia, occasional cases of nicotine poisoning, multiple sclerosis, and congenital abiopinaus may present reflex pupillary rigidity to light. These instances are, however rare exceptions. Riddoch points out that lethargic encephalitis and cerebral tumor involving the part of the midbrain concerned in the light reflex, may give the picture of Argyll Robertson pupil. Adie believes there is a benign syndrome of absent light reflexes and absent knee reflexes not due to syphilis. Menninger found only 34 per cent of the 176 abnormal pupil cases identified in 1000 examinations to be syphilitic —but he did not, apparently examine the spinal fluids. The importance of the encephalitis group of pupillary disturbances has certainly increased in the last several years. An enlarged left pupil, fixed to light, was recognized in a patient with absent Achilles reflexes and attacks of abdominal pain, simulating abdominal angina pectoris. The pain was later shown to be due to gallstones and absolutely no signs of either syphilis, encephalitis, or arteriosclerosis developed on complete examination and observation.

Adie's Syndrome (Pseudo-Argyll Robertson or Tonic Pupil).—In 1932 *Adie* described a syndrome consisting of tonicity of the pupils and absence of tendon reflexes which occurs in otherwise healthy and neurologically normal persons, mostly females. In its complete form one finds a combination of tonic convergence reaction, apparent absence of direct and consensual light reaction, and absence of tendon reflexes. In incomplete forms one may find (*a*) tonic pupillary reactions alone (*b*) atypical phases of tonic pupillary reactions alone; (*c*) atypical pupils with absent tendon reflexes; or (*d*) absent tendon reflexes alone. Adie pupil is frequently unilateral (80 per cent of cases, Kennedy Wortis, Reichard and Fair, 1938) and is usually dilated. The convergence reaction which is normal or hyperactive in Argyll Robertson pupils is tonic in Adie's syndrome, *i. e.*, one finds strong contraction of the pupil on convergence and for several minutes after it has ceased. While the Adie pupil appears to be lightfast in ordinary testing of the light reaction, if the patient remains in the dark quarter hour or longer the tonic pupil gradually dilates and on exposure to strong light slow contraction sets in. The reaction to mydriatics while poor in the Argyll Robertson pupil is normal in Adie pupil. There is no hereditary factor in Adie's syndrome nor any relationship of this syndrome to syphilis. It may be due to partial degeneration of the post-ganglionic fibers from the ciliary ganglion to the sphincter muscle (Scheie, 1940; McKinney and Frocht, 1940; E. Spiegel, 1941; Lowenstein and Friedman, 1942; Dynes, 1942.) Ophthalmologic consultation is desirable.

The rechecking of doubtful cases by complete syphilological examination has convinced us that it is safer for the diagnostician to regard pupillary disturbances as presumptive of neurosyphilis and to trace this possibility to the ground by adequate study than to accept too readily the likelihood of occasional exceptions. A spinal fluid examination and a complete serological and neurological examination are *sine qua non*.

Isolated Pupillary Signs and "Tabes Imperfecta."—It should not be too readily concluded that the isolated pupillary abnormality without other signs or symptoms, is merely a scar and that the process which brought it into existence is inactive or burnt out."

Dreyfus, in 1918, as result of thorough study of series of cases to which, however only short course of treatment was given, concluded that in 35 to 40 per cent of such cases the pupillary anomaly was residuum of previous "saturation of the nervous system by the infection, and that it was not, in such cases, necessary evidence of an active process. Nonne personal observations

lead him to the belief that there exists distinct type of "tabes imperfecta in which isolated pupillary anomalies, even coexistent with an abnormal spinal fluid, may remain nonprogressive over period of many years if not for life. He concludes with definiteness, on the basis of completely studied case with autopsy that if the spinal fluid be normal in the presence of an isolated pupillary anomaly the syphilitic process may be regarded as healed. This, it seems to us, is still *sub judice*, in view of growing evidence of the fact that negative spinal fluid is entirely compatible with progressive and serious neurosyphilis.

Pallor of the Disks.—Somberg in 2000 syphilitic patients with paretic symptoms found 4.2 per cent to have pallor of the disks which went on to optic trophy in 20 per cent. In 60 per cent of the group, however the fundus picture of optic atrophy was not followed by functional impairment even over period of two years.

None the less, Nonne's warning that slight fluid abnormalities accompanying isolated pupillary changes must not be too unfavorably interpreted in estimating prognosis is a valuable caution, for examples of negative fluids with isolated pupillary disturbances and apparently completely quiescent or "cured" infections, especially in women, do occur

The Seizure or Convulsive Attack.—This is one of the common symptoms of diffuse, or cerebrospinal, and of paretic neurosyphilis. It may appear within a few months after infection in precocious cases, or after a lapse of many years. Prodromal or abortive seizures may recur for years before coming to full intensity or the first attack of the apoplectiform type may be fatal. Localizable types, with the characteristics of jacksonian epilepsy and nonlocalizable types, indistinguishable clinically from idiopathic epilepsy are recognized. The frequency of seizures in neurosyphilis is a matter of dispute.

Nonne, while unable to offer figures of his own, contrasts the views of Neanya who saw only one example in 105 cases, and Heubner who saw 28 examples in 45 cases of cerebral syphilis. Southard and Solomon quote Kraepelin as finding 30 to 40 per cent of seizures in paresis, and 65 per cent of paretics were found to have had seizures on admission to the Munich hospital. Our own observations on general material showed 9 per cent to have suffered loss of consciousness, and among known neurosyphilitics, largely nonparetic, 6 per cent to have had epileptiform convulsions or petit mal attacks.

The description of various types of seizures given by Southard and Solomon is excellent, and is quoted verbatim.

"The most frequent seizures are epileptiform and bear resemblance t cortical epilepsy; but more rarely these seizures resemble the ordinary epileptic attack or consist of general shaking of the whole body A variety of initial minor disorders usher in the attacks; the temperature is often increased. The attacks are over after one or at most, few hours. Kraepelin speaks of one that lasted fourteen days. Sometimes *status paralyticus develops, suggestive of the status epilepticus*. Another rare form of characteristic seizure is the apoplectiform, which can hardly be told from an ordinary stroke, and may be followed by the usual postapoplectic phenomena. A good many of the strokes leading to sudden death in middle life are probably cases of neurosyphilis, although often set down as early arteriosclerosis of nonsyphilitic nature. Besides the epileptiform and apoplectiform seizures, there are certain seizures of less definite and complete nature, ranging from simple fainting spells, dizzy spells and petit mal ttacks to various special forms of irritative muscular contractions and temporary speech disorders. Sometimes these attacks occur with complete preservation of consciousness. Transient paresthesias, visual field defects, and especially ttacks of vomiting which, according to Kraepelin, may precede paresis by years (of course in this connection gastric crises of tabes must be thought of), may be counted as sensory seizures.

Paralytic phenomena may assume the form of monoplegias affecting single member or limb, or group of muscles in the face or elsewhere, or they may be true hemiplegias with complete involvement of one side. The onset may be sudden, or gradual, extending over weeks or months. These symptoms are usually the result of regional obliteration of the vascular supply of special areas with resultant softening, or of the invasion of the area by gummatous infiltration, either within the brain tissue itself or from the enveloping meninges.

The immediate prognosis of the epileptiform seizures in paretic neurosyphilis, without treatment, is good but it is a distinctive feature that with each attack the recovery only carries the patient to a point somewhat short of the recovery which he made from the preceding attack. There thus ensues a cumulative deterioration, with ultimate complete degenerative and fatal outcome. According to Southard and Solomon, no gross pathologic change can be recognized in the vessels and membranes, the pathologic change being evidently one of microscopic injury

Braetsch and Bahr (1937) reported 5 cases of syphilitic epilepsy in 4 of which multiple gross lesions of the brain cortex were present which were due to syphilitic vascular disease. In the fifth patient microscopic areas of softening in the central convolutions were associated with syphilitic endarteritis of the cortical capillaries. The pathology in all cases was characteristic of the meningovascular type of neurosyphilis. Epileptiform seizures, usually of petit mal type, are an annoying residue of otherwise reasonably successful treatment of cerebral neurosyphilis, particularly juvenile paresis in occasional cases under our observation. They are controllable by sedatives but may be part of a slow deterioration.

Speech Disorders.—These include especially aphasia and the dysarthria of the paretic. The former is, of course, a function of damage to a particular cerebral area, and hence chiefly associated with vascular gummatous, and meningeal lesions It has been our experience that the fugitive, transient, incomplete aphasic attack with recovery repeated again and again from an otherwise clear symptomatic sky has a more unfavorable ultimate prognosis than the sharply defined single attack from which recovery is slow or imperfect. It may precede by years the appearance of true paretic changes.

In studying speech symptoms care must be taken not to read aphasia into every moment of confusion due to fatigue alarm, language difficulty weakness, deficient thought control and nervous exhaustion, especially in taking the medical history The effect of nervous excitement in accentuating symptoms of this sort, is pronounced, and we have known them at the first interview t give an entirely false impression of the patient condition.

The dysarthria of early paresis is essentially a slurring of words. Together with relaxation of the facial muscles it makes a combination that arouses suspicion on sight.

So long as the patient retains the clipping sharpness of his speech one is tempted to say from therapeutic experience at least, that degenerative changes are still in the future. When the tongue begins to loll around the words, elisions to appear in the syllables, and the base of the tongue is swallowed in the effort to articulate a sentence, paresis has really begun. The test phrases, emphasizing the "r" are the ones which most quickly bring out significant defect—"truly rural, and "third riding artillery brigade. The implication of the tongue innervation and musculature in tic-like spasm is certainly suggested at times by the way in which the patient will bring the tip of the tongue forward by licking or sucking the lip, and then manage to bring out the phrase more nearly intact The effect of practice at repeating test phrases in reeducating the patient with insight to pronounce them better must be considered in estimating improvements based on speech changes It is better to depend on conversation than tests in observing the patient' progress.

Speech defect secondary to outright paralysis, as in the recent hemiplegic, must also be distinguished from the dysarthria of paresis.

Cerebral Neurasthenia.—The neurasthenic syndromes of syphilis have in our experience with the medical recognition of neurosyphilis, been among the chief sources of diagnostic error The distinction from true neurasthenia is undoubtedly at times extremely difficult to draw and there will be occasions when even the conscientious examiner will hesitate at carrying his study to the point of spinal fluid examination in a patient who offers no suggestive clinical or anamnestic signs. Yet it may be confidently asserted that nervous breakdown in middle life is so frequently a stalking-horse for paresis, and for

less fatal though ultimately incapacitating syphilitic lesions of the nervous system, that spinal fluid examination, to say nothing of routine and repeated blood serologic tests on all patients with nervous breakdown, can scarcely be too often resorted to. When syphilis is suggested at any point Nonne has well phrased the situation by saying that "a neurasthenic with syphilis in his history suggests a paretic." In all such cases examination of the spinal fluid is imperative. All syphilitic neurasthenia is not, however incipient paresis, as will subsequently appear

The multiplicity of somatic and psychic symptoms to which neurosyphilis can give rise affords the widest possibilities of error Of some of these possibilities the cases cited offer interesting examples.

Fig. 738.

"LATENT" SYPHILIS

Male, laborer, aged thirty

Chief Complaint: Pain in the knee, three months duration.
History Pain and stiffness of gradual onset. One month ago railroad doctor told him he had syphilis, but gave no treatment. Knows nothing of any infection, but had gonor rhea eighteen months ago. General health excellent.
General Examination Some grating in knee, no pain or tenderness, no limitation of motion, no swelling. Ray negative. Serum Wassermann positive. Result distrusted, but was positive on repetition. Referred to syphilologist.
Neurologic Examination Congenital divergent strabismus, slight pupillary irregularity neurologic examination negative.
Cerebrospinal Fluid (done routinely ... kh second arsphenamin injection) WR ///; Nonne positive; lymphocytes 18 1; colloidal gold 5554333810.

No Examination for Syphilis or of Syphilitic is Complete Without Full Study of the Spinal Fluid.

Backache simulating sacro-iliac strain, headache, ill-defined paresthesias, and often conspicuously gastro-intestinal symptoms, may dominate the scene, all to vanish on the institution of effective treatment for the underlying neurosyphilis. The tendency to dismiss from observation with reassurance only an apparently neurasthenic patient who has negative physical and elementary laboratory examination, stands next to inadequate physical examination, the over looked blood serologic, and neglected spinal fluid test, as cause of error Periodic reexamination will still make reasonably early correction of an error possible.

On the other hand hasty diagnosis of neurosyphilis from gastric crises to paresis should not be made in the absence of clinical or laboratory evidence of syphilis in patients with tension syndromes, anxiety neuroses, focal lesions of infective nature and vagus-sympathetic disturbances leading to spastic functional symptoms, etc.

It is unfortunately impossible to point to a distinctive symptomatology for syphilitic neurasthenia (Fig 739)

Fournier emphasized syphilitic insomnia; the early appearance of increasing difficulty of concentration, and the memory loss for recent events are frequently spoken of. Crises of confusion, depression, hyperactivity flightiness, and even maniacal excitement may occur Tremor especially of the lips, often seems an early warning. Riddoch states that the headache of the neurasthenic is discomfort, that of the syphilitic pain. None of these items has pathognomonic value.

The ultimate resort must be the painstaking history the thorough-going physical and the neurological examination, repeated blood Wassermann tests, the spinal fluid examination, and insistence on observation.

Delusions, character change, and what Southard and Solomon very aptly term *conduct slump* may precede by months and even years the appearance of gross symptoms of cerebral or paretic neurosyphilis.

These early and often insidious mental changes form the basis for business upheavals and collapses, family tragedies and crimes of violence occurring seemingly without medical or social background. An increasing expansiveness, accompanied by a diminution of critical faculty or merely increasing egotism with decreasing justification, such as one sometimes associates with the presenile state, develops. Exultations and depressions may become gradually more pronounced and causeless. An overgrown tendency to enter upon new enterprises at an age when conservatism usually comes to the fore, inability to see obvious obstacles, overliberal speculative use of resources in the face of existing responsibilities may be the first warning of impending trouble. The handwriting signs of omitted letters and words and tremor may be detected in the patient's signature, business correspondence, and check writing. Causeless rages directed against children or animals may early attract attention, although the patient may remain for a long time amenable to reason and repentant after each outburst. The sudden slackening of a previously rigid sexual morale may be a significant symptom. Before diagnosis becomes apparent the patient may be involved in

Fig. 729

"NEUROSIS AND OVERWORK" IN MIDDLE LIFE

Man, aged forty-five.

Chief Complaint. For several years has been having backache, pain in abdomen and rectum, headache, lassitude, sore throat, constipation, nervous breakdown eight years ago. No energy, especially in damp weather. Loss of weight.
Operations. Appendectomy for abdominal distress, no relief. Dilatation of sphincter and curettage of rectum for rectal distress—no relief. Tonsillectomy for sore throat—no relief. Turbinectomy for headache—slight relief.
Significant findings first examination. Liver palpable, eyes negative (refraction only), ears negative, rectum negative, but sphincter relaxed. Redundant sigmoid.
Diagnosis (3/29/16). Neurosis, overwork, needs vacation.
Overlooked in First Examination. Wassermann; history of venereal warts and gonorrhea, leukoplakia, pupillary reactions and deep reflexes.
Additional symptoms on return (6/17/16). Numbness, cushion feet, urine hard to start.
Additional findings on return. Unequal, slow pupils, absent right patellar, left Achilles reflexes, positive Babinski, joint sense —3.
SWR. Negative.
Spinal Fluid. WR *+++*. Nonne positive. Cells 8. gold sol 0012333100.

bigamy or be pilloried by a breach of promise suit. Carelessness in the details of dress and toilet may become apparent before any definitive signs sufficient to bring the patient to the physician appear. The "spotted waistcoat" goes with the increasing flabbiness of mental and physical tone. Persecutory ideas (paranoid state) may after a considerable period of silent brooding, come suddenly to the front in a single phrase or outburst that may subside again only to take form months later in some well-directed attack upon an object. The comparative clearness of the mental background from which explosions may sometimes arise well emphasizes the care that should be taken in releasing from custodial control the cerebral syphilitic who has once shown definite signs of persecutory delusions. J.H.S. has received telephone warning in the small hours of the early morning that a former patient, released long before from a state asylum after symptoms of mental disturbance due to neurosyphilis, by no means distinctively paretic in type, had just attempted the cutting of his wife's throat with the family carver and was on his way for medical advice. The intellectual "front" of such a patient may be unbroken a moment before such an occurrence; the tearful depressed or even the morose neurosyphilitic may be less dangerous.

Caution in Interpreting Early Mental Signs.—It should be emphasized that there is little of absolute specificity in any of these early signs. They may in mild forms be the earmarks of arteriosclerotic degenerations, the cap-

illary thromboses emphasized by Alvarez of encephalitic processes other than those of syphilis, of cerebral neoplasms, and of nonparetic syphilitic as well as true paretic dementia. None the less they may come early to the attention of a careful medical examiner and demand further study including at least a blood serologic test, a checking of pupils and reflexes, and further observation. The entire picture rather than the isolated details makes the diagnosis. Foster Kennedy's emphasis on fatigue is summarized below

In taking the history of such patients indirect evidence from the statements of others should be examined critically with respect to motive, for friends, associates, and even marital partners may have personal reasons for prejudiced testimony or may be unduly suggestible. The physician may at times be made the tool of a scheme to secure a power of attorney, the sequestration of a wealthy person, or the replacement of a chief by some ambitious and unprincipled subordinate. In critical cases involving important persons and interests the slowing down of the process of examination to allow time for better acquaintance with the patient himself, and a development of his confidence in the examiner may lead to valuable clues and correct mistaken impressions.

The Common Objective Signs of Neurosyphilis.—Among the important objective signs of early neurosyphilis, the sensory changes detectable by neurological examination take a place comparable to that of pupillary abnormality. It is a mistake to limit the search for these signs to the obviously tabetic or paraplegic case. They furnish some of the earliest warnings, especially of thoracic and lumbar cord and sensory root involvement, even in the seemingly healthy individual. The tendency of these changes is to appear earliest in the regions supplied by the lower segments of the cord, *e. g.* over the feet, legs, and thighs, and the lower thorax and abdomen. Sensitiveness to pin-prick especially should be carefully tested for the "islands" of analgesia, sometimes but not always symmetric, may be less than a palm-breadth in diameter. Gordon Holmes emphasized the dissociation of sensation, so that while a patient may exhibit an analgesia to pin-prick in a given area, his reaction to touch or to heat and cold may be normal or much less reduced. Reduction in vibratory sense as obtained with the tuning-fork (C 128) over the tibia and the malleoli, and decreased sensitivity of the Achilles tendon on pinching are common and suggestive early changes. In higher cord involvement and basilar lesions the upper extremities and the face are more affected, but it is not unusual to see the most extensive sensory changes in patients whose subjective symptomatology suggests only lower cord involvement.

Loss of the sense of motion and position, which means essentially that the patient, with his eyes closed, cannot tell where his members are or in what direction they are moving or being moved, is the basis of tabetic ataxia, and may be early detected by finger-to-nose and heel-to-knee tests, and by having the patient describe the direction of movement of a passively moved member with eyes closed. In the latter case it is important not to permit a clue to "leak through" by way of the pressure sense.

The importance of a sensory examination of the patient with early neurosyphilis is not alone diagnostic, but serves a valuable purpose as a base-line in subsequent rechecking of the progress of his disease, which, as we have mentioned, may take place in spite of a negative spinal fluid examination, and be evidenced only on his sensory chart and in his increasing disability. Unfortunately the detection of these finer sensory changes calls for experience and practice, and should not be too rashly undertaken by the practitioner.

The Romberg test and ataxia can be observed in any office examination. The patient should be questioned as to the onset of unsteadiness on the feet

when he is deprived of his sense of sight, as, for example, in washing the face or after dark. In doing the test the patient stands with toes and heels in contact and eyes closed He should be protected from falling As a remedy for the inclination of an oversuspicious examiner to interpret the slightest wavering in the patient, the checking of normal persons, and an occasional test on himself will not come amiss. Unsteadiness in standing on one foot with eyes closed must be interpreted with caution. The ataxia of the tabetic may range from the slightest tendency to come down hard on the heels and to separate the feet in walking, to almost a total paraplegia, in which the knees cave outward and the sole slaps the pavement with a resounding thwack, the foot being thrown ahead almost as an inert object. The spasticity of combined sclerosis may first appear in the toe gait or steppage or be recognized by slight stiffness in gait and slight tremor and tension of the calf muscles. The halt foot limp or slight dragging of the foot and the slightly flexed arm on the same side may be the first sign of a slowly developing hemiplegia, or the residuum of an acute accident. The wearing of the toe of the shoe on the affected side may be early noted Tests for ankle clonus and plantar flexion of the great toe (Babinski) and "push-and-pull" and "hand-grasp" tests of muscle power on each side detect the beginnings of these changes

As in the case of test phrases in detecting speech defect it is possible for the patient with ataxia to improve himself by practice and thus to vitiate the effect of subsequent tests by a succession of examiners.

SEROLOGICAL FINDINGS IN NEUROSYPHILIS

After reference to foregoing discussions and especially to Chapters IV and XII (early neurosyphilis) the serological status of neurosyphilis as a guide to clinical neurosyphilis may be reviewed from Figs. 740–741

Menninger and Bromberg (1935) found among 400 cases of various types of neurosyphilis with positive spinal fluids that 31 per cent gave negative blood serologic reactions and 69 per cent gave various grades of positivity (44 per cent, "4 plus") In an extended study of the serology in general paresis, Blalock and Hesse (1938) noted that of all patients, irrespective of the kind of treatment they received, 8 1 per cent had a negative blood Wassermann reaction prior to therapy. This corresponds with the 8 6 per cent of paretics untreated with arsenicals with positive spinal fluids and negative blood serologic reactions observed by Kierland, O'Leary and Vandoren (1942) or to the 10 4 per cent in paretics treated with arsenicals prior to the tests.

Provocative Reaction in the Spinal Fluid.—Inasmuch as clinical symptoms may be lacking, the provocative spinal fluid test may become an important factor either in diagnosis or in determining the activity of a known syphilitic process apparently quiescent on ordinary examination. The unreliability of the provocative effect on the blood should be recalled P 77

The observations of Solomon have been confirmed by subsequent reports and by our own experience. Cestan, Riser and Bonhoure in a study of 69 cases found that in no case was a provocative effect on the spinal fluid, either in the form of a positive Wassermann reaction or an increase in albumin or lymphocyte count obtained in the absence of syphilis, or in syphilis devoid of previous clinical or serological evidence of the disease The activation of a negative fluid occurs only when neurosyphilis is present, and may be produced by as little as a single injection of neoarsphenamine although several injections may sometimes yield a delayed positive result.

The delay occasionally observed in appearance of the provocative effect is in keeping with the slower reaction and greater inaccessibility of the nervous

system and has been confirmed in our experience. It is best for this reason to perform the spinal test at the end of a complete provocative procedure, seven to ten days after the arsphenamine injection, or even later to detect the development of positive signs.

Costan et al. find reactivation of the Wassermann reaction to be the most frequent occurrence. They believe the spinal fluid provocative test to be of principal value in determining the status of seemingly inactive or "burnt out" neurosyphilis, of asymptomatic cases, and of

Fig. 740.

FREQUENCY OF COMBINED NEGATIVE BLOOD WASSERMANN AND NEGATIVE SPINAL FLUID IN SYPHILIS IN GENERAL

	Per cent.
Early cases	16
Treated cases after second year	47
Late syphilis	16–18
Untreated syphilis	4–7

These estimates are based on the summaries of Stokes and McFarland, Stokes and Brown, Stokes and DesBrisay and Fordyce and Rosen, aggregating 1635 cases.

patients who have been under treatment. Dunlop could find no evidence of nonspecific provocation of positive Wassermann reaction in the spinal fluid by the administration of neoarsphenamine.

It is important to stress the fact that the slightest suggestion of a provocative effect in a quiescent neurosyphilis should be followed by enough treatment to insure against a dangerous revival of activity and that a second examination some months later is needed to determine the return of the fluid to normal. Otherwise there may ensue the dangerous "reactivation" of the process, as emphasized by Ravaut and others.

Fig. 741.

FREQUENCY OF A NEGATIVE SPINAL FLUID IN UNDOUBTED NEUROSYPHILIS

	Per cent.
400 patients with preponderantly late syphilis had neurosyphilis in	73
400 patients with preponderantly late syphilis had abnormal CSF in	63
Proportion of negative spinal fluids in neurosyphilis	*13*
405 patients with neurosyphilis (treatment study) had negative CSF in	7
76 patients with tabes dorsalis had negative spinal fluids in (Walker and Haller)	16

The Spinal Fluid Wassermann.—The most frequently quoted interpretations of blood and spinal fluid Wassermann tests in late syphilis are those of Nonne, who very properly laid much stress upon the amount of spinal fluid used. He all but suggests that the strongly positive Wassermann reaction on 0.2 cc. of spinal fluid is one of the earmarks of general paralysis. He obtains from 85 to 90 per cent positive Wassermann reactions in this concentration in paresis as against 20 per cent in tabes and 20 to 30 per cent in cerebrospinal syphilis. On the other hand, with 1 cc. of spinal fluid most tabetics yield positive Wassermann reactions; paretics and taboparetics are practically invariably positive, and patients with cerebrospinal syphilis also yield almost 100 per cent positives. Gennerich stresses relatively low proportion of positive spinal fluid Wassermann reactions in combined tabes and myelitis. One of the most interesting groups of figures (Fritzsche)

ness with a consequent decline in social status, has aptly been designated by Collins as "psychic scar" and occasionally occurs in vascular syphilis. Cases seemingly typically vascular at the outset, may go for years without other signs, ultimately only to pass over into general paresis.

Fig. 744.

CHARACTERISTICS OF PARALYTIC ACCIDENTS IN VASCULAR NEUROSYPHILIS

Paralyses may be partial or total, mono-, hemi-, or triplegias.
Onset may be sudden, but is often gradual with gradual recovery.
Gradual ascending or descending paralysis may occur.
May be no signs of insult such as loss of consciousness, convulsions, etc., even in sudden and total paralyses.
Lesions may be central, not cortical.
Triplegias are uncommon; both extremities of one side, one of the other.
One paralysis may follow another or convulsions may affect a previously paralyzed limb.
Marked tendency to recovery is the rule; rarely fatal. The commonness of thrombosis as contrasted with arteriosclerotic hemorrhage is the explanation.
Aphasia is common often with a monoplegia or hemiplegia or seventh nerve paralysis. Usually motor in type and transient.
Bulbar symptoms may develop from thrombosis of the frequently involved basilar artery; ocular paralyses, disturbance of speech and swallowing reflexes, with crossed paralysis of the extremities.
No sensory disturbance in most cases.
Pupillary changes usually absent (uncomplicated cases).
Occasional central hemianopsia.
Serology: Blood usually positive, spinal fluid negative or only slightly abnormal (Type I).

Fig. 745.

DIFFERENTIAL CONSIDERATIONS IN VASCULAR NEUROSYPHILIS

Patient too young for arteriosclerosis.
Syphilitic history may be obtainable (or may not).
External collateral signs of syphilis are likely to be lacking.
The blood serologic reaction may be positive (or may not).
The spinal fluid examination may be positive (or may not).
The therapeutic test may be meaningless (spontaneous recovery).
The diagnosis may have to be made by exclusion:
No gross arteriosclerotic signs (inspection, palpation, blood-pressure).
No demonstrable renal insufficiency (uremic hemiplegia or convulsions). Urine and blood were normal.
No cardiac lesion to explain thrombosis or embolus.
No acute infection.
No disease causing vascular injury: Leukemia, pernicious anemia, diabetes, alcoholism, metallic poisoning (arsphenamine, etc.).
Among the possibilities consider: Arteriosclerosis, idiopathic apoplexy in youth, brain tumor; multiple sclerosis, uremia, hysteria, migraine with hemiparesis, general paralysis, solitary tubercle of the pons, heart disease in young syphilitic patients.

Cerebral Meningeal Neurosyphilis.—The symptomatology of cerebral meningeal neurosyphilis is outlined in Figs. 746 and 747.

In order to facilitate comparisons, the symptomatology of meningitis of the convexity of the brain is given in Fig. 747 also by recalling that the two processes may combine, and especially so in the later cases. In general, as one reviews the chronological perspective of neurosyphilitic lesions, those of the base and particularly of the optic and the seventh and eighth nerves, a

might be expected, appear more conspicuous early in the disease, while the nuclear lesions come to the front later

Importance of Recognizing Prodromes.—It is apparent that meningitis of the convexity with its essentially nonspecific symptomatology can be much more readily diagnosed objectively

Fig. 746.

SYMPTOMATOLOGY OF BASILAR MENINGITIS

Headache: Usually severe; pain deep in the eyes, sensitive to percussion over the brows.
Dizziness and Vomiting Not unusual and not distinctive.
Stupor or Excitement: Elaborate psychotic disturbance rare and usually due to combination with other lesions.
Fever: Not unusual, but apt to be atypical. Occasionally but rarely high, rarely subnormal temperature.
Optic Neuritis and Papilledema: Most important nerve lesion, more frequent than in any other form of brain syphilis. Examination of both fundus and fields essential.
Ocular Muscle Palsies Partial oculomotor (N III) palsies the commonest type, ptosis, diplopia, pupillary disturbance, strabismus. Total third nerv paralysis (accommodation also) usually late. Ptosis the commonest symptom. Combined pupillary and accommodational disturbance suggests tabes or paresis (Nonne)
Other Cranial Nerve Lesions: The combination of second and third nerve lesions with those of other cranial nerves suggests cerebral syphilis as against tabes dorsalis.
Polyuria, Polydipsia, Pituitary Syndromes Relatively rare may take the form of diabetes insipidus, infantilism, dystrophia adiposogenitalis, etc.
Symptoms of Bulbar Lesions and lesions of the ninth, tenth, eleventh, and twelfth cranial nerves rare. Glycosuria, central deafness, trapezius paralysis, tongue paralyses, etc.

when combined with enough basilar involvement to supply the more distinctive signs of cranial nerve palsies. Combinations with vascular lesions may materially increase the complexity of the picture without altering its general trend. In If it may be quite impossible to separate meningeal from vascular symptoms, and only the outstanding localized lesions will be clinically identified by the average physician. The emphasis should be placed on the similarity of the early symptoms

Fig. 747

SYMPTOMATOLOGY OF MENINGITIS OF THE CONVEXITY

Headache Diffuse or localized, often boring; frequently but not invariably worse at night patient may seem deafened.
Tenderness on Percussion: May be localized over special area of the skull; not pathognomonic.
Attacks of Dizziness Occasionally the chief or only complaint.
Vomiting Not specific in character but sometimes suggesting the crises of tabes dorsalis.
Pupillary Anomalies Occasionally Isolated symptom.
Psychic Disturbances: Resemble those in vascular syphilis of the brain neurasthenic symptoms, occasionally delirium suggesting infection, more frequently progressive dementia, apathy amnesia, inertia and hebetude, altered personality and retarded (not aphasic or dysarthric) speech.
Papilledema or Choked Disk: Occasionally
Epileptiform Convulsions Generalized or jacksonian, or both combined frequency matter of dispute.
Hemiparesis and Paralysis Rarely monoplegias.
Cortical Speech Disturbances Aphasia, short duration, incomplete, speech groping. Associated with motor disturbances of face and extremities.
Hemianopsia Rare

and prodromes of the various later and more serious changes in both vascular and meningeal syphilis of the brain. No persistent or severe stupefying headache should ever escape at least the check of blood serologic test, nor should negative result be uncritically accepted. Alterations of personality and neurasthenic beginnings should not be dismissed as overwork or "nervous breakdown, nor mental disturbance be given merely symptomatic label without review of the possibility of syphilis, regardless of the person involved Resort should be had more fre-

quently in the consideration of all affections of the nervous system, to the steps of an elementary neurological examination which identify partial palsies and reflex changes, and to a search for pupillary and fundus signs whose importance is paramount in the symptomatic picture of treatable cerebral syphilis. Even granted some initial opposition to a spinal test, the physician can in most cases, once a definite neurological complex becomes apparent, secure consent to clear the diagnosis at once by a properly performed serological examination if no contraindications exist.

Acute syphilitic meningitis, while unusual, is not excessively rare. It is essentially the homologue of acute syphilitic nephritis and acute syphilitic hepatitis. Fahr case developed in the ninth week after infection, with fatal result. The 5 cases which Stokes has seen, while less fulminating, had the classical signs of acute meningitis, including headache, Kernig sign, neck rigidity and fever but without delirium or pupillary changes. The spinal fluids in all cases showed turbidity and cell counts over 1000 per cubic millimeter. The negative smear and culture and the positive blood and spinal fluid Wassermann established the diagnosis, and recovery took place under mercury and iodide, followed by arsphenamine.

Merritt and Moore (1935) in an important study of the literature and 80 cases of their own found that from 0.2 to 5 per cent of cases of early syphilis develop meningitis. Most of the cases occur within the first six months of the infection in patients who are untreated or inadequately treated. These authors describe 3 groups. (a) Acute syphilitic hydrocephalus (26 cases): These patients have headache, nausea and vomiting, choked disks and meningeal signs (involvement

Fig. 748.

RELATIVE FREQUENCY OF INVOLVEMENT OF THE VARIOUS CRANIAL NERVES IN SYPHILITIC MENINGITIS*

Cranial nerve.	Involvement per cent.
I	1.5
II	20.0
III	23.0
IV	2.5
V	11.0
VI	21.0
VII	40.0
VIII	41.0
IX X	6.0
XI	0.5
XII	3.5

* Merritt, H. H. and Moore, M. Acute Syphilitic Meningitis, Medicine 14: 119–183, 1935.

of posterior fossa interfering with the circulation of the cerebrospinal fluid and causing internal hydrocephalus). (b) Acute vertical meningitis: Headache, nausea and vomiting, convulsions or mental symptoms indicating involvement of the meninges over the vertex of the brain. (c) Acute basilar meningitis: cranial nerve palsies indicating involvement of the meninges at the base of the brain. (See Fig. 748.)

The blood serologic tests are positive in 60 per cent of the cases. Pleocytosis in the spinal fluid is moderate or marked (25 to 2000 cells). The spinal fluid Wassermann is positive in 90 per cent of the cases and spirochetes have been found in the fluid.

Psychic Scar in Meningeal Neurosyphilis.—Meningeal, like cerebral vascular syphilis, may produce the picture of healing with defect even in cases exhibiting a minor subjective symptomatology at the outset and making an apparently rapid response to treatment both clinically and serologically. The impression may be one either of unfavorable progress or the onset of paresis. The picture may appear to change from one form of disability to another or from a minor form such as a cranial nerve palsy to a major one of profoundly altered personality as the patient "recovers." In this way a business man of fair capacity may be transformed into a mediocre day laborer as his disease comes to a standstill. Such homologous paradoxic exaggeration of signs in the

process of healing is, of course, familiar in cardiovascular syphilis. It is necessary in cerebrospinal syphilis to make frequent allowance in prognosis for those large, "silent," and inaccessible portions of the nervous mechanism whose condition cannot be seen or tested for but which may provide a degenerative aftermath that mars recovery

THE CLINICAL PICTURE OF GENERAL PARALYSIS (PARESIS) OF THE INSANE

The foregoing summaries have made it apparent that not every syphilitic patient who has mental symptoms is *ipso facto* a paretic. Syphilis of the brain has a fairly rich psychotic background from which paretic neurosyphilis can be separated in some cases with ease, in others only with the greatest difficulty if at all.

Fig. 749.

CLINICAL CLASSIFICATIONS OF GENERAL PARALYSIS

Nonne.	Hecht (161 cases, 128 males)	Per cent men.	Per cent women.
1. Typical paralysis	1 Simple dementia	66 5	65 7
2. Lissauer' focal paralysis (vascular changes)	2. Agitated and expansive	18 8	17 9
3. Atypical paralysis	3. Depressive	5 7	10 2
Catatonic.			
Senile.			
Fulminating.			
4. Stationary paresis	4. Circular	3 3	2 6
	5. Galloping	3 8	None.
	6. Atypical (paranoid and hallucinatory)	3 3	None.
	7 Undetermined	4 1	2 5

The characteristics of the syndrome were first established by Alzheimer and Nissl, and two clinical classifications are given in Fig 749

The pathologic changes themselves vary as widely as the symptoms, as Solomon has pointed out, even in cases receiving diagnosis of paresis t competent hands. The main pathologic essentials include diffuse inflammatory reaction in the cerebrum, chronic spirochetal encephalitis, localizing about the vessels and meninges, with coat-sleeve lymphocytic and plasma-cell infiltration about the capillaries and degeneration of the parenchymal cells ith compensatory gliosis. These elements vary in their relative proportions, so that in some cases extreme atrophy and little inflammatory change is apparent, in others the vascular picture and plasma-cell infiltrations are prominent. So-called atypical general paresis" would appear from the analysis of Hermel to include nearly every known pathologic change associated with such an infection as syphilis, including miliary gumma and endarteritis with and without the demonstrable presence of *Spirochaeta pallida*.

Even though we can no longer make a fatal issue the test of the diagnosis of paresis, it is certainly possible to say that syndromes with very different onsets and symptomatology and with extraordinarily long and extremely short courses, with and without remission can none the less end in the symptomatic picture of paretic dementia and paretic neurosyphilis. Thus one may observe a "vascular" type of paresis, in which the progressive deterioration

is punctuated by typical accidents, transient or permanent. One sees patients who have typical basilar meningeal lesions cleared up by treatment, who yet, after periods of years of seeming symptomatic inactivity go into paretic decline One finds paretic dementia run the *slow* course of arteriosclerotic senility or sees arteriosclerosis, in the absence of syphilis, produce excellent imitations of paretic dementia. Even the strongly positive serological findings of paresis which have held out best and been most emphasized as diagnostic criteria in recent writing on neurosyphilis may occasionally *fail* in practice



Fig. 750.—*Treponema pallidum* in brain tissue from general paralysis. Stained by Nageotte's method of silver impregnation of nerve tissue (× 1000) (Collection of Dr Nageotte.)

and paresis with negative blood serologic reaction, and even with negative spinal fluid after treatment, be proposed for consideration. While nondescript symptoms or neurorecurrence presents the serology of paresis with complete recovery or as in tabo-paresis with optic atrophy with symptomatic arrest.

Symptoms of "Typical" Paretic Neurosyphilis.—In presenting a symptomatic summary combined from several tables by Southard and Solomon and our own experience therefore it should be understood that only a central core is proposed whose possibilities of confusion with the general territory of

meningo-vasculo-parenchymatous neurosyphilis are apparent enough when Fig 752 is compared with those which have preceded it.



Fig. 751 —Granular ependymitis in the floor of the lateral ventricles. The patient had a "paretic" spinal fluid, but no symptoms, and an advanced aortitis unrecognized during life.

Fig. 752.

SYMPTOMATOLOGY OF PARETIC NEUROSYPHILIS

Amnesia: Especially for recent events.
Consciousness clouded; intake impaired, *fatigability* increased, hallucinosis rare.
Judgment impaired; oversuggestibility fantastic delusions, grandiose, paranoid; insight into illness, slight or nil.
Quick-shifting Emotions.
Irritability or Hebetude.
Character Change.
Conduct Slump Violent rages, sexual escapades and excesses.
Nervous Disorders: Headache, visual disturbance, tremor ataxia.
Speech Disorders Dysarthria, aphasia, vocal change.
Writing Disorders Tremor omission of letters and words.
Pupillary Changes: Argyll Robertson pupils, pupillary irregularities, transient anisocoria. Pupillary changes may occasionally be slight.
Reflex Changes Exaggeration most common (taboparesis excluded)
Seizures Epileptiform, hemiplegic, aphasic, most typically transient and repeated.
Facies: Flattened nasolabial fold, Relaxation, mental "let down," tremulousness, vacuity
Serologic Picture Strongly positive blood and spinal fluid Wassermann, positive globulin, cell count under 100, repeated first zone colloidal test. (Type III.)
Paralyses and Contractures (late).

The pupillary changes, including Argyll Robertson pupils, associated with paresis, are not necessarily sufficient to identify the clinical combination known as taboparesis, and form, therefore, an integral part of the picture of paresis. Joffroy found pupillary changes in part as follows in a series of 300 cases of general paresis (Fig. 753) (*cf* Adie's syndrome)

Foster Kennedy in an admirable brief address (Brooklyn Soc. of Int. Med.) summarized some of the clinical simulants of paresis as follows: effects of great fatigue, even to slowing of the pupils (during the First World War); lead intoxication; intestinal intoxications in middle life; arteriosclerosis. His suggestion that a test of the paretic is to require him to write not a line or two, but a *four-page letter* is most useful.

One cannot exclude paresis merely by the fact that the time interval between the chancre (if one had occurred) and the appearance of clinical signs is short, since true paresis may develop, as soon as eight months (Zeifert, 1939) or as long as thirty years (average fifteen years) after infection. Cheney (1933), however, found only less than 2 per cent of his cases developed after a latent period of less than five years. Fifty-seven per cent came on after a latency of ten to nineteen years and 6 per cent in over thirty years.

Trauma and General Paralysis.—The influence of trauma as a factor in syphilis is considered in Chapter I. Its importance in paresis (especially head injury) is discussed by Klauder and Solomon (page 15) and Merritt and Solomon (1943). Trauma may apparently incite to paretic manifestations a neurosyphilis that would otherwise have remained quiescent. The fact, now accepted, has important medicolegal and industrial liability bearings.

Fig. 753.

PUPILLARY CHANGES IN GENERAL PARESIS (AFTER JOFFROY)

	Per cent.
Altered light reflexes	73
Pupillary inequality	65
Lost light reflex	[illegible]
Irregular pupils	[illegible]
Diminished accommodation reflex	17
Mydriasis	13

Course of Paretic Neurosyphilis.—The course of paretic neurosyphilis varies remarkably in different patients. An acute *fulminating* or *galloping* form occurs, with an encephalitic picture and fever (Cestan and Riser) or with rapidly successive seizures or shocks, each leaving the patient more deteriorated than the preceding, and terminating *often* in the fatal convulsive state already mentioned. The excited type with flight of ideas, delusions, extreme irritability and outbursts of maniacal violence is contrasted with the silent, depressed and suicidally inclined patient, and with the slow deteriorative type which gradually declines into silliness, dementia, and amentia. The *mental characteristics which constitute the average conception of paretic* neurosyphilis belong simply to a median type whose euphoria, fabrication, and grandiose delusions during a physical decline unaccompanied by any consciousness of course or termination, is the medical apotheosis of an easy death. Less than three to six months, in extreme cases, three to five years in average cases, and five to thirty or more years in the unusual slowly deteriorative type (Galbraith, 1940) is an all-round prognostic scale.

Remission, a feature of paresis to which much interest attaches, is an as yet unexplained phenomenon. It consists in a spontaneous *temporary recovery* often of astonishing completeness, from all active symptoms of the disease. Remission occurs, according to various authors, in from 4 to 17 per cent of

untreated cases (Cotton, Gaupp, Kraepelin) Its duration may range from a few months to as long as twenty-two years in the extraordinary case observed by Tuczek, the average duration being from six months to a year

Four of Nonne 10 apparently cured cases in premalarial days turned out to be examples of long remissions. Remission, according to Kraepelin, is more common in the agitated and expansive types than in the depressed and demented forms. Improvement may be very sudden, but restoration to entire normality is rare. The patient may treat his past with certain degree of insight, but more often slurs over it, and tremor and speech defect residua may be detected on examination. The improvement in the flabby relaxed, and vacuous facies of the paretic and the restoration of crispness to the speech in remissions produced by treatment are most interesting to watch.

The possibility of remission complicates all decisions regarding the effect of treatment and the curability of the disease.

Paresis Sine Paresi.—Just as isolated pupillary signs may precede by years, and absolutely without other event, the appearance of general paresis, so the spinal fluid may during a long asymptomatic period, present the strongly positive Wassermann reaction on all concentrations, positive globulin, pleocytosis and first zone colloidal reaction of general paresis, in combination with positive blood serologic reactions. This serological forerunner of clinical paresis has been designated by Solomon "paresis sine paresi" and has been spoken of in an earlier chapter as the "red flag. (See also asymptomatic neurosyphilis.) While it does not have infallible prognostic value and while such fluids may appear early in neurorecurrence, and respond to treatment there is much reason to believe that the repeated serological findings of "paresis sine paresi" in successive examinations is of grave prognostic significance. *We have been inclined to limit the term to cases in which such fluid findings* withstand vigorous treatment, rather than to apply it on the outcome of one or two examinations.

Senile Paresis.—This is name applied to picture suggesting arteriosclerotic dementia which characterizes paresis beginning late in lif (Bennett, Riser and Gay). The condition makes no response to treatment and is rapidly fatal. Diagnosis depends mainly upon serological findings.

OTHER SYPHILITIC CEREBRAL SYNDROMES

Brain Gumma.—Brain gumma is not as specific a term as tradition supposes, and its symptomatology is, therefore, ill-defined. Miliary gummas if numerous give the symptomatology of diffuse neurosyphilis of an encephalitic type. Gummatous infiltration may also assume a diffuse form. Sharply defined solitary gummas may present the localizing signs of brain tumor if in an area from which such signs can arise. In the frontal lobes they may produce the entire range of mental symptoms given in Fig 752. Accompanied as they often are with meningeal thickening and inflammation, or originating in some cases in the meninges and invading the brain substance, they may present in addition to the pressure symptoms of brain tumor (headache, vomiting, and choked disk) the paralyses of ocular muscles and involvement of cranial nerves which assist in identifying a meningitis. Solitary gumma may exist without an abnormal lumbar spinal fluid, so that negative findings from this *angle do not necessarily exclude brain gumma from the diagnosis.* The blood serologic reactions may be, but are not necessarily positive A Wassermann test on the ventricular fluid, obtained at operation, may yield a positive finding, although the lumbar fluid may be negative.

Gumma of the hypophysis, especially of the anterior lobe, is stressed by Simmonds and Nonne as frequent in prenatal syphilis, and very responsive to treatment. Involvement of the infundibulum has also been recently illustrated by cases reported by Lhermitte and Kyriaco (narcolepsy diabetes insipidus, obesity amenorrhea) and by Louris (diabetes with pigmentation, enlarged liver and dysendocrinism), Brugsch, Lewi and Dresel (midbrain sclerosis with diabetic syndrome). We have seen amenorrhea and pituitary obesity in congenital syphilitic woman simulate pseudocyesis. The precaution taken in the preserological era, of invariably giving a course of potassium iodide to all suspected cases of brain tumor before the relief of pressure symptoms by trephine, if time permitted, deserves revival in the light of the inadequacy of the serologic test in this diagnostic field. Trephine does not necessarily come amiss in gumma with pronounced pressure symptoms, but the surgeon should restrain desire to go too far if signs of marked pachymeningitis are encountered.

Brain tumors of nonspecific origin may occasionally respond temporarily to modern syphilotherapy so that the diagnostic resort in the individual case must often be determined by the seriousness of the patient's condition and the presence of localizing signs which will direct an intelligent surgical intervention.

Acute Syphilitic Encephalitis.—Disseminated syphilitic encephalitis, an unusual and still debatable entity may be confused with lethargic encephalitis and with the hemorrhagic encephalopathy of arsenical reaction

The patient in Fig 436 came to his death in what may have been this fashion in the third year of his infection, after neurorecurrence which had apparently been brought under control by treatment. The infection in Barrett's case was only of seven months duration, and occurred in the prearsphenamine era. The onset is sudden, with clouding of consciousness, lapsing rapidly into stupor or for a brief period with noisy delirium and restive movements. Localizing signs do not at first appear but after the first twenty-four to forty-eight hours it may be possible to identify pupillary anomalies, beginning ocular muscle palsies, and peripheral paralytic changes. These seldom become marked before death occurs. In our patient, as in Barrett's, the cortical lesions were more marked than in the usual lethargic encephalitis. The spinal fluid and blood Wassermann reaction in our case were repeatedly negative. To assert that the condition in our patient is syphilitic merely on the basis of a history of syphilis and recent neurosyphilitic involvement does not, of course, bear critical examination. No spirochetes were found in the brain in Barrett case in subsequent examination, and none could be found in the brain, spleen, liver, or lymph nodes examined in our case. It is therefore entirely possible that the case was one of infectious encephalitis of nonsyphilitic origin. (Sugar in spinal fluid 0.15 Gm. per 100 cc.)

Subacute or Chronic Syphilitic Encephalitis.—That encephalitis in syphilis does not necessarily follow an acute course, as described above, is suggested by several cases we have been called upon to treat. Their symptoms on admission were stupor and disorientation, amounting almost to coma, but with no distinctive signs of a meningeal or vascular lesion. In one case the spinal fluid was negative in another strongly positive A third case at first supposed to be encephalitic subsequently developed hemiplegic accidents indicating vascular basis not at first recognized Recovery with psychic scar resulted in the first two, but the time under observation is, of course too short to determine their ultimate outcome. In one instance the presence of a weakly positive spinal fluid Wassermann reaction, in patient whose history and course were typical of postinfluenzal encephalitis, well illustrated the caution which must be used in interpreting encephalitis across which the suggestion of syphilis has been thrown either by history or signs. The encephalitic syndromes so frequently described since 1918 have greatly increased the possibility of confusion.

When an acute encephalitic picture in a neurosyphilitic follows upon an arsenical injection, the difficulty in deciding whether the condition is a therapeutic shock (Herxheimer) a hemorrhagic encephalopathy or a syphilitic encephalitis is considerable The attempt to give adrenalin in one such case as a therapeutic test provoked a violent exacerbation from which the patient fortunately recovered

Syphilitic Pseudoparesis and Nonparetic Syphilitic Dementia.—These terms apply to the borderland of paresis, and are in all probability variations on the symptomatic pictures of meningovascular brain syphilis which suggest paresis, but do not follow the classical course to fatal termination. Nonparetic dementia of syphilitic origin often has negative spinal fluid, and may well be product of cortical vascular changes. Kraepelin gave to nonparetic syndrome characterized by auditory hallucinosis, delusions of persecution, and peculiar suddenness of onset and remission the name *syphilitic paranoia*. The status of the disorder is uncertain according to Southard and Solomon, and not based on complete serological evidence.

Encephalomalacia in Syphilis.—Widespread degenerative and atrophic changes, *secondary to innumerable foci of atheromatous change affecting the* finer vessels of the brain, give rise to a clinical picture that may be interpreted either as meningovascular neurosyphilis, as an atypical paresis, or even as tumor of the cortex, though the latter is eliminated by the absence of pressure signs.

In a most striking example, this confusion in diagnosis was well illustrated by the contrast between the clinical diagnosis of vascular neurosyphilis on the basis of five years observation of repeated hemiparetic seizures with a negative spinal fluid, made in the Mayo Clinic and the equally insistent diagnosis of typical general paresis by asylum physicians based upon the terminal picture. The autopsy disclosed almost unbelievable encephalomalacia with profound arteriosclerotic changes in the basilar circulation.

SYPHILITIC SPINAL CORD SYNDROMES

Separate description of cord and cerebral lesions in neurosyphilis can be excused only on account of convenience, for the two processes are rarely sepa rated in fact. It is apparent from our account of the general symptomatology of neurosyphilis that cord symptoms come much more to the front in ordinary practice than do cerebral symptoms. This is readily accounted for by the *relatively large silent areas and larger tissue reserve of the brain, as contrasted* with the intense concentration of the transmitting and controlling mechanism of the cord. Certain it is that cord complaints outnumber cerebral complaints in the patient s story ten to one, and testify continually to the practical truth of the statement one of us (J H S.) has several times made, that neurosyphilis (*i. e* cord syphilis) is in reality the syphilis of internal medical practice, *for it is the source of innumerable and too often inexplicable symptoms* in gross examination.

Pathology—An important anatomic consideration influences the pathology and symptomatology of cord lesions in syphilis. The vascular distribution of *Spirochaeta pallida* deposits it, obviously in those parts of the tissue most directly supplied by the principal vessels of the arterial system. These are the posterior portions of the cord, including the posterior meninges, the sensory horns, and the posterior and lateral columns of the cord. The anterior or motor horns are much less frequently affected. Thus sensory rather than motor disturbances characterize large part of the symptomatology of spinal syphilis. Even those symptoms which appear clinically to be motor in character are often in reality due to disturbances of the sensory segment of the reflex arc. There are of course, exceptions in the myelitic pictures which will appear in due course

The cord and its meninges are subject to the same pathologic changes which characterize all syphilis of the nervous system—acute and chronic syphilitic inflammation, and the *meningeal, vascular gummatous, and parenchymatous degenerative lesions* previously described. Taken as whole the white matter is more frequently involved than is the gray matter of the cord (Nonne).

Vascular Syphilis of the Cord.—The principal syndrome is that of throm bosis of the anterior spinal artery (Spiller Margulis, Ornsteen *cf* S Berman

1940 below Merritt, 1940 and King, 1942) with apoplectiform onset, complete flaccid paralysis of trunk, arms and legs, and loss of deep reflexes when upper levels are affected. Absence of direct violent trauma, rapid progress, no prodromes, are important in diagnosis. A stationary is followed by a spastic stage

Fig. 734

EARLY SYMPTOMATOLOGY OF SYPHILITIC SPINAL MENINGEAL AND MENINGOMYELITIC LESIONS

Pain: In the neck, between the shoulders, in the back or lumbosacral region (backache, "sacro iliac strain, etc.")
Paresthesias and Pains in upper or lower extremities and buttocks.
Hyperesthesia in spots where pain is felt.
Tenderness on pressure in the hyperesthetic areas.
Muscular tension May reach the point of contracture.
Increased tendon reflexes.
Stiffening of the back Chiefly on rising Nocturnal pain not especially characteristic.
Secondary symptoms from spinal nerve involvement: Sensory changes, slight paralyses (may be "pseudo" due to fear of pain)
Early bladder disturbance: One of the earliest and most important myelitic symptoms.
Motor weakness, often interpreted as fatigue.
Spinal fluid: Strongly positive in all reactions, blood Wassermann usually positive.

Meningitis and Meningomyelitis.—Figure 734 presents the symptomatology of spinal irritation, the prodromal complex of many meningomyelitic lesions.

The advance of the process with the sharper definition of level signs brings out the *paraparesis and paraplegia of the upper or lower extremities*, the *dissociation of sensation*, in which pain and temperature senses are modified or lost first while other forms persist unchanged and *ankle clonus Babinski sign*, and *further exaggeration of tendon reflexes*

Fig 735.

SPECIAL SYMPTOMATOLOGY OF CERVICAL MENINGOMYELITIS

Paraparesis and spastic later flaccid paraplegia of all four extremities.
Signs of involvement of the brain, especially:
- **Headache and dizziness.**
- **Aphasia.**
- **Unilateral paresthesias** of the extremities.
- **Pupillary changes and extra-ocular paralyses.**
- **Optic neuritis.**

Cervical Sympathetic Symptoms Unilateral pupillary contraction, sweating, and redness of skin
Fluctuation in th extent and intensity of symptoms.

In lumbar cord involvement the development of a chronic myelitis results in the disappearance of reflexes and a flaccid paralysis ensues.

The picture of pachymeningitis hypertrophica cervicalis in syphilis is essentially as in Fig 735 The involvement of the upper extremities may be more marked than the lower and the cerebral symptoms less conspicuous.

This syndrome of chronic hypertrophic cervical pachymeningitis as well as that involving other levels of the spinal cord is well portrayed by Wilson, Bartle and Dean (1939) and by King

(1942). Wilson and his coworkers from study of 18 cases point out that no symptom or syndrome may be regarded as pathognomonic. From their cases syphilitic pachymeningitis, although showing an affinity for the cervical and dorsal regions, cannot often be regarded as an exclusively localized process, but rather as regional manifestation of usually more generalized meningovascular syphilis. In 10 of their 18 cases definite brain symptoms were clinically manifest.

Syphilitic Transverse Myelitis.—The pathologic changes involved in syphilitic transverse myelitis may include, in one and the same case, vascular inflammatory and gummatous processes. Acute and chronic forms are recognized The acute form is sudden in onset and within a few hours may reduce the patient to a helpless paraplegic. *Nonne gives the frequency in his practice* as 8 cases in 212 of spinal syphilis.

Acute accidents may occur in the course of a chronic myelitis. In this case they are preceded by prodromes similar to those in Fig 756 The bladder in such cases may show retention for a considerable period.

Nonne states that the appearance of paralytic signs from level different from that which the prodromal symptoms lead the observer to expect, is suggestive of syphilis. A fluctuating course is more suggestive of syphilis than of the nonspecific types. The suddenness with which

Fig. 756.

SYMPTOMATOLOGY OF SYPHILITIC ACUTE TRANSVERSE MYELITIS

Onset sudden, progress rapid.
Upper extremities rarely affected.
Total paralysis lower trunk and extremities.
Sensation totally lost or dissociated remnants may persist.
Total incontinence of bladder and bowel, or retention followed by incontinence. Pyelitis usually follows.
Edema of the extremities, occasional.
Decubitus, sacral, of fulminating onset.
Loss of tendon reflexes, if lesion is below the center
Exaggeration of tendon reflexes, if lesion is above the center
Rapidly fatal course, in most cases.
Spinal fluid and blood usually positive.

decubitus develops in these cases is sometimes almost unbelievable. Stokes has seen the sacrum and both trochanters virtually denuded of overlying soft tissues by huge slough within three or four days, in spite of every precaution; this in striking contrast to the ordinary infectious or toxic myelitis of his experience.

Acute syphilitic transverse myelitis in the early months of a syphilitic infection may have a more favorable prognosis than the late type. Cole has reported with bibliography a case occurring in the second month of the infection with recovery under treatment with mercury and arsphenamine and Stokes has seen a case also recovering under mercury and arsphenamine which occurred nine months after infection. Remains of the patient s grouped follicular secondary syphilid were still present.

S. Berman (1940) in well documented report of case notes that judging by the frequency of published reports acute syphilitic transverse myelitis is becoming rare. From 1924–1940 only 5 cases have been reported in this country

Syphilitic Spinal Paralysis (Erb s Syphilitic Spastic Paraplegia)—This syndrome has been a storm center of controversy since its description by Erb in 1892 The question is essentially whether the picture is not simply that of

a chronic incomplete dorsal myelitis as in the case reported with microscopical study by Collins and Taylor or that of a transverse myelitis. There is also question as to its invariably syphilitic character. Nonne compromises, after a summary of the literature, by saying that there is such a disease but that it may be the result either of lateral or combined sclerosis, or of myelitis. Spastic symptoms appear in various syphilitic syndromes, including general paralysis, and it is interesting to see one competent observer make a diagnosis of Erb's spastic paralysis while another simultaneously makes a diagnosis of paresis, the latter supported by the course and outcome. Many early paretics, before mental changes are well defined though recognizable exhibit the curious symptom of "spastic thumb" in which under examination tension they exhibit a "splayed" or hyperextended thumb and at times a positive Babinski and ankle clonus.

Peters (1941) studied the blood and cerebrospinal fluid serologic findings in 30 cases of Erb's syphilitic spinal spastic paraplegia. He found the blood serologic reactions for syphilis positive in 73.3 per cent of the cases, while the cerebrospinal fluid was normal in 23.3 per cent of the cases. (Type I 13.3 per cent, Type II 20 per cent and Type III in 36.6 per cent.) In only 3 patients was serologic evidence of syphilis completely lacking. King (1940) in his monograph on "Syphilis of the Spinal Cord" summarizes this condition as follows: "This syndrome is not common, it occurs five times more frequently in males and is sometimes a late complication of syphilis. Clinically the patients present a picture of slowly developing weakness, fatigue and stiffness of the legs, with little or no pain. Bladder disturbances are frequent. Examination reveals spastic paraplegia with evident lateral column damage but little or no sensory loss. At first there is paraplegia in extension, but this later may occasionally become paraplegia in flexion. There is no block in the subarachnoid space. The condition has to be differentiated from cord tumor, multiple sclerosis, other forms of cord involvement due to syphilis, and changes due to pernicious anemia. The blood and spinal fluid Wassermann reactions are frequently positive but may be negative. The process is very resistant to treatment and frequently progresses in spite of it."

Fig 737

SYMPTOMS OF ERB'S SYPHILITIC SPINAL PARALYSIS

Onset gradual, some years after infection.
Spastic paresis of the lower extremities.
Spastic gait.
Little true motor paralysis.
Little increase in muscle tonus.
Increased tendon reflexes.
Little or no sensory disturbance.
Slight or moderate bladder disturbance.
Pupils, cranial nerves, upper extremities, psyche and intelligence unaffected.

The obvious problems in differential diagnosis raised by the cord lesions of the anemias and multiple sclerosis can only be answered by the spinal fluid examination and complete study of the patient for other signs of syphilis.

Acute Ascending Spinal Paralysis (Landry).—Nonne and Spiller maintain that Landry's paralysis may be of syphilitic origin in some cases. The clinical features of the Landry type of spinal paralysis consist of ascending paralysis of the spinal and finally of the bulbar nerves, with preservation of sensation and electrical reaction but disappearance of reflexes. Care must be taken not to confuse the picture in some cases with that of syphilitic polyneuritis, in which, however, marked sensory changes and disturbance of electrical reactions do occur.

Amyotrophic Lateral Sclerosis.—Kalber has extensively discussed syphilis of the spinal cord manifesting itself in the clinical picture of amyotrophic lateral sclerosis. Stone rates syphilis as

the most common cause of chronic spinal progressive muscular atrophy of the atonic type. Early and vigorous antisyphilitic treatment may arrest the wasting and weakness.

Syphilitic Chronic Anterior Poliomyelitis.—Syphilitic involvement of the anterior horns, while uncommon, occurs either alone or occasionally in abortive form (upper extremities) in combination with tabetic changes in the lower cord.

The syphilitic factor in spinal muscular atrophies must be borne in mind even though the picture be not typical of anterior horn involvement.

Nonne discusses the literature with reference to amyotrophic lateral sclerosis and the Aran-Duchenne type of progressive muscular atrophy quoting among others, Dana (prESerological period, 1906) who found 25 per cent of such patients to have syphilitic histories. Spiller emphasized the importance of histologic findings in his cases.

Syringomyelic Syndromes.—Syphilitic meningomyelitis, with the production of compression symptoms and invasion of the cord by solitary gummatous infiltrates, may occasionally give rise to isolated paralyses with regional dissociation of sensation momentarily suggesting syringomyelia.

Brown-Séquard Syndrome.—This picture may be produced by gummas which invade the cord from the pia-arachnoid, causing unilateral lesions. The cases may be regarded clinically as cord tumors and may involve any portion of the cord. Nonne rates the lesion as rather-common one among the pure cord involvements, citing also Oppenheim and Mitchell Clark. The symp-

Fig. 736.

SYPHILITIC CHRONIC ANTERIOR POLIOMYELITIS

Pain, insistent and severe, in the affected extremities.
Weakness of the peripheral muscles.
Atrophy often beginning in the small muscles of the hand, sometimes selecting groups of muscles, sometimes the extremity in toto.
Fibrillary twitching of the affected muscles.
Changes in electrical reactions.
Preservation of sensation.
Isolated loss of reflexes.
Final complete paralysis and paralytic atrophy of the affected muscles.

tom complex consists of motor paresis or paralysis of one side of the body usually chiefly the lower extremity with loss of pain and temperature sense on the other side. The picture, when syphilis is responsible, is often imperfect, the patient having paraparesis with accentuation of the motor phase on the one side, and more marked sensory dissociation on the other, though both sides are somewhat affected by both types of changes. Signs such as pupillary abnormalities, suggestive of more extensive neurosyphilitic changes, may also be present. The therapeutic test may be of importance in differentiation.

The Combined Scleroses.—The vascular supply of the cord is such that a variety of combined column degenerations are possible, among which the combined sclerosis of the posterior and lateral columns is the most common and easily recognized. The clinical picture includes mixtures of varying proportions of tabes dorsalis and spastic paraplegia, so to speak. Abortive forms of tabes, with pupillary rigidity to light, optic atrophy extra-ocular muscle palsies, lightning pains and sensory disturbance, will be associated with increased instead of lost tendon reflexes, ankle-clonus, positive Babinski sign, and a slightly spastic gait becoming ataxic with the eyes closed. The preservation of sexual power in a patient with the eye signs and lightning pains of tabes should lead at once to a search for the earmarks of lateral column involvement. Pupillary changes may appear late instead of early

TABES DORSALIS

Fundamentally tabes dorsalis is a disease of the dorsal roots of the spinal nerves, with ascending degeneration of the posterior columns of the spinal cord (Goll and Burdach) Occasional muscle atrophy has been explained both as due to anterior horn cell and to parasympathetic involvement (Cadwalader 1932) The clinical symptomatology is directly derived from these facts, although the clinical variability of the sensory and subjective picture sometimes makes it difficult for either physician or patient to realize the unity of the process.

Whether or not tabes dorsalis, like paresis, is to be regarded as primary syphilis of the nervous system in the sense that syphilitic meningitis is a primary syphilitic process caused directly by *Spirochaeta pallida*, or whether it is to be regarded as secondary degenerative picture possibly of toxic origin (para or metasyphilis) cannot be discussed here, and is still the field of marked differences of opinion.

That tabes is not a disease of the sensory nerve roots and the spinal cord alone, but is, in reality a cerebrospinal process is evident not only from such symptoms as Argyll Robertson pupil, extra-ocular muscle palsies, and primary optic atrophy but also from the combinations which it presents with paretic neurosyphilis (taboparesis) While, therefore, we may describe for convenience a "typical tabes dorsalis," an uncomplicated picture will be anything but the rule in ordinary practice, and too much rigidity should be guarded against in diagnosis. On the other hand, if single symptom of tabes, such as pupillary rigidity to light, be selected as diagnostic, the field of tabes becomes almost synonymous with all of neurosyphilis, to say nothing of many nonsyphilitic neurological conditions. The student should therefore guard against making part of the picture stand for the whole.

Tabes as a Deficiency Disease.—*Because of its current influence* on treatment conceptions, the hypothesis that tabes is at least partially a nutritional or vitamin deficiency disease should be specially mentioned Much of the reasoning is based on the importance of avitaminoses, particularly A and B complex in conditions such as pernicious anemia, beri-beri and syndromes experimentally produced in animals but as yet without parallel in man, in which a degenerative type of change in nerve tissue and recovery under adequate diet or vitamin therapy are well recognized This subject has been well reviewed by Moore and Woods (1940) and Cochems and Kemp (1942) chiefly in conjunction with primary optic atrophy and lightning pains. Metildi (1939) used the work of Wintrobe Mitchell and Kolb (1938) as the basis for his introduction of thiamine chloride into the treatment of tabetic pains. Stone (1942) employed vitamins B and E intrathecally and cited Reese and Hodgson s (1939) preliminary feedings of the B complex to tabetics with ensuing improvement prior to antisyphilitic treatment. Conceptions of the role played by vitamin deficiency must be regarded as still in the formative stage and the multiplicity of action of such highly complex agents as the vitamin groups constantly kept in mind in interpreting mechanisms. When a vitamin group like B which relieves constipation, acts as an antiallergic, assists in controlling intestinal infection influences secretion of hydrochloric acid in *hypo- and achlorhydrica and so forth, is employed in therapy* interpretations of mechanism are hazardous. When the crystalline vitamins are employed, the results are less clear-cut (Cochems and Kemp, B) and it will be necessary to test out individually riboflavin pantothenic acid (calcium pantothenate), and pyridoxin at least in response to various suggestions as to which item or combination of items seems to be therapeutically useful.

Symptoms of Tabes Dorsalis.—The symptomatology of tabes dorsalis will

vary with the stage of the process in the material surveyed (Fig. 759) A num ber of them, especially of the sensory type, have been described as early symptoms of neurosyphilis.

The proportions of various symptoms are dictated to some extent by the stage of the disease in the material studied. Early cases show a lower propor tion of ataxia and rombergism and a higher proportion of pains and pares- thesia. No single symptom or sign of tabes is, of course, diagnostic, but groups of two or three taken together should arouse enough suspicion to lead to a search for the entire picture. The atypical character of tabes dorsalis in women is a point which has been of much value in clarifying our experience. The incomplete forms, especially with reflex eye disturbances, a few "rheumatic"

Fig. 759

IMPORTANT SYMPTOMS AND SIGNS OF TABES DORSALIS

Symptoms.	Per cent.
Lightning pains	73–90
Visual symptoms	44
Difficulty in urination	43–68
Trouble in starting.	
Dribbling afterward.	
Nocturnal frequency and "bed-wetting	
Paresthesias (numbness, prickling, girdle sensation, etc.)	40–58
Ataxia	57–87
Strabismus	18
Diplopia	11
Girdle sense	10–31
Visceral crises (gastric, rectal laryngeal)	10–22
Loss of libido and potentia	6–25
Failing vision	6
Ptosis	5–23
Vertigo	4–12
Deafness	1–4

Signs.	Per cent.
Argyll Robertson pupils	80
Reduced or absent lower cord reflexes	70–90
Romberg sign	43–86
Sensory disturbance and dissociation	40–68
Diminished pain.	
Diminished vibration sense (bone fork conduction).	
Diminished sense of motion and position.	
"Cord" (atonic) bladder	45
Trophic changes	12 19
Charcot joints.	
Malum perforans.	
Optic atrophy	6–9
Miscellaneous, including muscle trophy tabetic clubfoot, wrist and foot drop, hyperextensibility of joints (decreased muscle tone) mentioned by various authors.	

Combined from the statistics of Nonne, Lecke, and Stokes and Shafler aggregating approximately 1400 cases and descriptions by Cad alader (1928), Windelman (1936).

pains, and slight frequency or dysuria but no ataxia, should not be too readily accepted as an "arrested" or "burnt out" neurosyphilis, a constant temptation to the internist or general practitioner who minimizes syphilis in his experience. A spinal fluid test may indicate an active process.

On the other hand, the negative spinal fluid in progressive cases, especially with trophic changes and crises, is too commonly misinterpreted in general diagnosis, especially where a surgical issue seems to be involved Not only the blood serologic reaction (often negative) and spinal fluid examination, but a neurological study with examination of the eyegrounds and visual fields, and even observation over a period of several years for signs of unfavorable prog- ress, are essential to the correct interpretation of incomplete tabetic pictures.

Gastric and Visceral Crises.—Three types of gastric crises have long been

recognized the attack of pain without vomiting the attack of vomiting without pain and the most common type, combining both pain and vomiting. Simons (1930) emphasizes the pain and hyperalgesia of the abdominal wall, without true deep pain or rigidity in the splanchnic type of crisis. Many gradations from abortive to severe forms exist. As a rule, the attack comes on without warning, though patients occasionally say they have had premonitory sensations. Exhaustion, emotional stress, acute infections and treatment shocks, including lumbar puncture may serve as precipitating incidents but, more characteristically the attack comes on from a clear sky The pain is usually epigastric, though the patient often has difficulty in defining or localizing it. It may radiate into the neck and jaw the back, chest, shoulder sacrum (Simons) may be intermittent or continuous. Intense nausea may be the only symptom. It is of agonizing intensity grinding or spasmodic, and soon reduces the average patient to convulsive sobbing helplessness. The vomiting is uncontrollable, and continues long after stomach and even duodenum may be emptied. The most trying feature is the nervous collapse and disorganization that often ensues during the several days to a week or more that the attack may last, resembling more than anything else the state of nervous collapse of a hypersensitive woman in childbirth. The recovery is almost as striking. The pain and vomiting disappear within a few hours, and the pale, exhausted and disheveled patient usually rapidly regains composure and appetite. The weight loss may be extreme and, in combination with exhaustion and loss of morale, constitutes the chief background for a fatal issue.

Woltman, grouped crises in the abdomen as: (1) sympathetic, with marked pain, vomiting and hyperalgesia over the abdomen, (2) vagal, with little pain, but marked nausea and vomiting, with pain in the region of the larynx, ear or heart; and (3) phrenic crises, with abdominal pain, hiccough and pain over one or other shoulder The pain of crises even when severe is strikingly unaccompanied by tenderness to deep pressure, though the patient may complain bitterly of the weight of a sheet or ice-cap

Roentgenologically and in tracings, the stomach is seen in violent contraction during crises which may be shared by the entire gut but it is not proved which (pain or contraction) is cause which is effect.

Simons (1930) gives an excellent review of the classification of gastric crises and conceptions of their pathogenesis. H interprets the crisis with nausea, vomiting, gastric hypersecretion without pain as of vagus, probably nuclear origin; that with severe pain and hyperesthesia of the abdominal skin, as of splanchnic type (paravertebral sensory fibres). The third is a mixed type.

The most striking symptomatic characteristic of the majority of gastric and other visceral crises in tabes is their periodicity which is sometimes as perfect as that of the menstrual function or of cyclic vomiting The tendency of the attacks is to follow closer and closer upon one another in the lapse of months or years, so that the patient ultimately can no longer recover his physical equilibrium between them He may pass over into a distressing state of almost continuous nausea. Laryngeal crises are of course marked by spasm with symptoms of suffocation that may necessitate tracheotomy Rectal crises are occasionally seen Differential diagnosis depends not upon symptoms, but upon the signs of neurosyphilis elicited by examination with elimination of other possibilities. More often after repeated misdiagnosis as gallstone attacks, the periodicity without apparent exciting cause arouses suspicion of gastric crisis.

Celialgia.—Turner uses this term for sensations of twisting, burning or heaviness in the epigastrium without radiation or vomiting, though with salivation or constipation, and diar-

acteristically pain on pressure over the solar plexus. Relief as well as diagnosis is secured by therapeutic test.

Achlorhydria, Pylorospasm.—Symptoms arising from or associated with either of these conditions may be interpreted as gastric crisis rather too easily in patients with syphilis plus functional neurosis. Objective evidence of neurosyphilis of tabetic type is necessary to diagnosis, and tabetics may have gastric neurosis symptoms without crises.

Errors in Medical and Surgical Diagnosis Associated with the Symptomatology of Tabes Dorsalis.—The rich visceral symptomatology of neurosyphilis, and particularly that of tabes dorsalis with its sensory root pathology provides an admirable background for general diagnostic error which has been illustrated by previous case records. It may be said in general that the internist meets with difficulties chiefly in dealing with the cerebral syndromes which suggest neurasthenia, while the surgeon encounters them in the symptomatology of tabes. Incomplete examination and unfamiliarity with the outstanding facts of neurosyphilology account for most avoidable errors. A systematic study by Nuzum of surgical error based upon the records of 1000

Fig. 700. (After Nuzum.)

USELESS SURGICAL OPERATIONS IN 1000 CASES OF TABES DORSALIS

Surgical diagnosis.	*No. of operations.*
Gastric ulcer	19
Gall-stones or cholecystitis	19
Appendicitis	18
Salpingitis	13
Exploratory laparotomy	9
Renal calculi	7
Postoperative adhesions	7
Tumor of cauda equina.	1
Sciatica (nerve stretching)	1
Meningocele	1
Ectopic gestation	1
Peritonitis	1
	97

cases of tabes dorsalis in the Cook County Hospital, Chicago, yielded a table (Fig 700) which outlines the main sources of error The proportion of tabetics subjected to useless operation amounted to 0 7 per cent.

Among the definite symptoms of tabes, visceral crises furnished 65 per cent of the occasions for diagnostic error Woltman found that crisis patients had received an average of two abdominal explorations each. Unbelievable persistence in error was well illustrated by a patient seen on our service in the Hospital of the University of Pennsylvania, whose abdomen carried five scars of laparotomies performed elsewhere, marking unsuccessful operations for gastric crises (Fig 701) We have never seen a surgeon who either makes an adequate examination himself, or acts upon the findings of a competent medical consultant, operate upon a case of gastric crisis under an erroneous diagnosis. If emphasis be placed upon the *signs* of tabes elicited in history and examination rather than upon the blood serologic reactions and spinal fluid examination both of which may be negative, this mistake will almost never occur

Taboparesis.—The syndrome of taboparesis is variously interpreted and in ordinary practice is earliest recognized as a combination of the objective signs of tabes with the spinal fluid and blood serology of paresis. This combination is particularly associated in our experience with primary optic atrophy and patients presenting it should have immediate field and visual



Fig. 701.—Pentalaparotomy for gastric crises.

This patient was first seen September 26, 1925 complaining of stomach pains of nine years duration occurring one to two times a week for which he had had four laparotomies. Primary lesion 1911 Previous treatment, 4 intravenous injections in 1921

Examination revealed irregular pupils which reacted very sluggishly to light and accommodation, and normal deep reflexes. Bladder tabetic in type but patient not incontinent. BWR negative CSF—strongly positive Wassermann increased globulin; 63 cells; and typical "tabetic curve After prolonged treatment with bismarsen, total of 67 injections, the abdominal pain was unrelieved.

CSF February 25 1928, Kolmer-Wassermann, 0134; increased globulin, 10 cells; mastic 4443210000.

Patient was lost sight of in 1928 and returned in September 1929 saying he had had an abdominal operation in an outside hospital.

In May 1939 patient was examined after ten years lapse. He had no gastro-intestinal complaints and the examiner stated that there seemed to have been "remarkable symptomatic improvement. Blood serologic reactions and spinal fluid examination negative

In May 1942, patient, now sixty-five years of age entered clinic looking and feeling well except for his old complaint pain in the stomach. This pain was worse after certain types of food. No changes in physical examination.

acuity studies and ophthalmoscopy of the fundi before any form of treatment is instituted Not uncommonly the mental degenerative features and symptomatology of paresis play the lesser role and with the onset of blindness, as Camp used to emphasize, the process comes to arrest without the typical paretic fatal termination.

SYPHILIS OF THE PERIPHERAL NERVES

Syphilitic neuritic disturbance if involvement of cranial nerves be excepted, is relatively rare form of syphilis of the nervous system. The following forms are well recognized:

Secondary Involvement of Nerves.—This is the result of pressure on nerves due to periostitis, or syphilitic osteitis of the vertebrae, and to gummatous processes involving lymph nodes, fasciae, and muscles. The diagnosis must be made through identification of the primary syphilitic cause

Syphilitic Root Neuritis.—This is rare condition, of which Nonne cites examples suggesting tumor of the cauda equina. The symptoms include paralyses of isolated muscles supplied by the involved nerves, pain, isolated reflex changes, weakness of the bladder and anal sphincter, and the spinal fluid findings if positive

Syphilitic Perineuritis.—This occasionally involves peripheral nerves and can be detected by beadlike thickenings, distortion of the trunk of the nerves, and more or less pain on pressure. The demonstration of syphilitic etiology must be by collateral factors. The nerves most commonly involved, according to Ehrmann, are the ulnar crural, and peroneal.

Syphilitic Neuralgia.—Nonne states that syphilitic neuralgias are most conspicuous in the early stages of the disease. Syphilitic trigeminal neuralgia presents no distinctive clinical features and can only be identified as syphilitic through general examination and history and its prompt response to treatment. Ornsteen has described isolated bilateral fifth nerve involvement. A case practically indistinguishable from tic douloureux, of nine years duration, associated with positive blood Wassermann and spinal fluid, with prompt response to treatment, is described by Vieta. Trigeminal neuralgia late in the course of syphilis is probably not of syphilitic origin though simulated occasionally by tabetic pains in this region and has usually required surgical treatment for relief although one of us (J. H. S.) has seen one striking exception. Cervical plexus neuralgia is likewise uncommon, though not rare. Intercostal neuralgia, with relapses and entire absence of other symptoms of neurosyphilis, may persist for years. Lumbosacral plexus neuralgia stands next in frequency to trigeminal neuralgia. Obstinate and severe sciatica may be one of the principal symptoms and nocturnal exacerbations are emphasized. The identification of the syphilitic cause for these conditions depends mainly upon serological and collateral clinical findings plus history of infection and response to treatment for syphilis. The almost invariable presence of tender point where the nerve emerges through the fascia, and the comparative lack or total absence of objective sensory changes in the course of the nerves are suggestive In one observed case the "sciatic pain disappeared permanently following hemiplegia, suggesting central factor

Syphilitic Neuritis and Polyneuritis.—The subjective symptoms of syphilitic types incline more toward paresthesia than toward actual severe pain. The attacks are rarely so prolonged or so severe as with other conditions. Neuromuscular hyperesthesia to pressure and spindle-like enlargements of the nerve trunk may be detected when the nerve runs superficial course. Motor paresis affects particularly the radial, ulnar and peroneal nerves. A variable degree of atrophy with diminution of the appropriate reflexes takes place. Involvement of nerve in the course of gumma may give rise to neuritic paralysis.

Polyneuritis is very much more common in syphilis than involvement of isolated nerves. A pure motor, sensory and pseudotabetic type have been described by Castan. An early acute form accompanying the cutaneous and osseous manifestations of the secondary stage clears up with extraordinary rapidity under mercurial and iodide treatment for syphilis, point of infallible differential value The extent of toxic versus direct spirochetal origin in this type has been argued as for all acute structural disease (syphilitic nephritis, hepatitis, etc.) in early syphilis. The occurrence of definite peripheral neuritis in an alcoholic patient receiving antisyphilitic treatment must not be confused with true syphilitic polyneuritis. The same applies to "foot-drop occasionally seen as complication of intra-arterial injection of heavy metal. A rare form of syphilitic root polyneuritis occurs in which cranial nerve paralyses and gradual extensive involvement of spinal nerves develops, which must be differentiated from the compression syndromes produced by syphilitic gummatous meningitis. The chief interest of syphilitic root neuritis lies in the simulation of tabes (Nonne).

DIFFERENTIATION OF NEUROSYPHILIS FROM OTHER NEUROLOGICAL CONDITIONS

Every neurological description properly emphasizes the fact that there is no specific cerebral or cord symptomatology in neurosyphilis if the items be taken individually A complete survey of the case must be made including the complete examination of the blood and spinal fluid and of the fundus and

Differentiation of multiple root neuritis and syphilitic polyneuritis is considered by Nonne (1921 edition).

fields of the eye and all the changes found must be taken into account. On the other hand, it may be said again that if the practicing physician can assemble a reasonable preponderance of ordinary clinical signs and convincing serological evidence in blood and spinal fluid for a syphilitic etiology he can usually proceed safely to treatment. The differential considerations here given apply to those pictures in which confusion is most likely to occur. Whenever ill-defined or doubtful cases in these types arise the inexperienced should seek advice.

Chronic alcoholism gives rise to conditions which *may easily be confused with neurosyphilis*. A history of total abstinence from alcohol eliminates them, but a collateral history of syphilis does not, since the two often coexist.

Pupillary irregularity and sluggishness, though not perhaps an absolute Argyll Robertson phenomenon, convulsions with a postconvulsive stupor, persistent amnesia, fabrications with euphoria ("liar dementia"), disturbance of reflexes, difficulty with test phrases, tremor, and writing disturbance, may all occur and differentiation from general paresis be possible only upon the finding of a negative blood and spinal fluid. It should be recalled that a gin debauch may lead to a temporarily negative blood serologic reaction. The dementias of chronic alcoholism and acute alcoholic symptoms occur in patients who, by virtue of their habits, may be expected to present higher incidence of syphilis than the average. For this reason the spinal fluid examination is particularly essential in all doubtful cases. The presence of cranial nerve palsies favors the diagnosis of syphilis. Signs of alcoholic polyneuritis may accompany the convulsions and mental disturbance (Korsakoff syndrome).

Alcoholic pachymeningitis can simulate pachymeningitis of the convexity, both giving rise to diffuse or localized headache, somnolence, and even to localized convulsions of the Jacksonian epileptic or general epileptic type with paralyses of the extremities.

Cerebral Arteriosclerosis.—The production of pupillary abnormalities and senile dementia by arteriosclerosis makes possible confusion with general paresis, on the one hand, and with abortive forms of tabes, on the other. The senile arteriosclerotic psychosis presents hemiplegic seizures, confusion, memory defect, deterioration of judgment, insomnia, and irritability. Southard and Solomon, who *describe very interesting* case in which the death of the patient who from general paralysis was the clue to the finding of a positive spinal fluid in the patient himself, state that small group of senile cases may present grandiose delusions. A high grade of frontal lobe trophy observed at autopsy as in a case of advanced cerebral arteriosclerosis seen on our service (myelomalacia) may suggest paresis on gross examination. Syphilitic arteritis and non-specific arteriosclerotic changes may produce an almost interchangeable clinical symptomatology associated with thrombosis of the basilar arteries. In such cases *only* combinations of the arterial process th signs of cerebral meningitis, positive blood and spinal findings, and collateral clinical evidence of syphilitic infection, can serve to distinguish the two. Nonne states that even Jacksonian convulsions and a *status epilepticus* may be simulated *by cerebral arteriosclerosis* in senile subject. The frequent failure of the spinal fluid in syphilitic vascular disease to show any distinctive reactions increases the difficulty of differentiation.

In spite of the foregoing considerations the student and practitioner should be cautioned *against too ready acceptance of marked grades of pupillary* abnormality in later life as merely arteriosclerotic in origin. They are much oftener suggestive of syphilis, and the specific possibility should be traced to the bottom.

Brain Tumor.—Opportunities for the confusion of brain tumor with cerebral syphilis are numerous in special practice, though fortunately brain tumor is much less common in ordinary practice. The first possibility arises in connection with headache, vomiting, and edema of the optic nerves as symptoms. It may be safely said that there is not single neurosyphilitic cerebral syndrome hich cannot be imitated by a properly localized brain tumor. Nonne emphasizes in discussing the psychic disturbances that the mentality of the brain tumor case is essentially torpor semisomnolent condition rather than the disturbances of consciousness observed in neurosyphilis. The possibility of confusing glioma of the frontal lobes with paresis in syphilitic patient is brought out in Fig. 774. Bilateral choked disk may of course develop purely as result of localized basilar meningitis, and in 1 case observed by Ayer† such picture had been produced by a *meningitis involving the chiasm*. The patient had undergone decompression for sup-

An elaborate differentiation of cerebral arteriosclerotic psychic disturbances from those of paresis is given by Weber (quoted by Nonne).

† Personal communication.

posed brain tumor (autopsy). Unilateral choked disk is more likely to be local meningeal phenomenon. Tumors of the base of the brain may be imitated by the hypophyseal syndrome of basilar meningeal neurosyphilis, including ocular nerve palsies and optic neuritis. The therapeutic test in distinguishing tumors from cerebral syphilis is not always reliable, for slow-growing sarcomas may show temporary improvement, optic neuritis may improve under mercury even though not of *syphilitic origin, and Fig. 774 likewise illustrates transient improvement of the* symptoms of cerebral gliosis. Nonne cites case in which convulsions following arsphenamine were interpreted as Herxheimer reaction in case of sarcoma. Under these circumstances only the ensemble of the evidence from history clinical findings, serological examination, and familial study can make an antemortem diagnosis possible. Exploration in patients with accessible localized lesions may be the best practice. It goes without saying that gummas of brain and meninges may themselves be brain tumors.

Brain Abscess.—Nonne insists that the confusion of syphilis and brain abscess will be largely prevented by withholding the latter diagnosis unless evidence of source of infection elsewhere in the body or of head injury can be found.

Dementia Praecox.—Very presentable imitations of the paranoid and catatonic types of dementia praecox can be produced by nonparetic neurosyphilis and by general paresis. Mention has been made of the occurrence of hallucinations and persecutory delusions in the latter condition, and the nonsensical flow of conversation of the paranoid dementia praecox may likewise occur in purely syphilitic psychosis. The physical signs may be insignificant, or the patient may seem entirely normal apart from his mental disturbance, yet the serological findings may be conclusive for neurosyphilis though not invariably for paresis. The symptoms disappear under treatment for syphilis. Nonne stated (1921) that he had seen no satisfactory examples of typical catatonia in neurosyphilis, but cites reported instances, and Southard and Solomon include in their series young woman of twenty-six (Case 66) who, following period of excitement and auditory hallucinosis, developed typical catatonia, resistiveness, and noncooperation. The positive spinal fluid and blood Wassermann findings were confirmed by autopsy at which a syphilitic encephalitis as found. In practice the differentiation must be made on the general picture and the serological findings. Nonne observed dementia praecox in patients with congenital syphilis, but sees no reason for ascribing direct syphilitic etiology to the condition. Healing with *defect, familiar in dementia praecox, occurs, of course, in neurosyphilis, as previously stated.*

Manic-depressive Psychosis.—The possibilities of confusion of cerebral neurosyphilis with manic-depressive psychosis are numerous and the differential diagnosis from variety of angles admirably discussed by Southard and Solomon. According to these authors laboratory tests furnish the final diagnostic criteria in most cases, but they of course, do not eliminate manic-depressive psychosis as complication of neurosyphilis. The depressive state appears to be the more difficult to differentiate, and no qualities seem to be wholly sufficient to distinguish the depression of general paresis from that of manic-depressive psychosis. Pupillary signs and speech defect if present are of great value, but may be absent even in advanced cases of cerebral neurosyphilis. A history of manic-depressive psychosis in the family and of previous alternating excited and depressed phases of conduct, in some cases antedating syphilitic infection, is of value. In the manic phase differentiation of the two types of disease may be equally difficult since identical delusions may occur in both. As Nonne says, only years of observation may decide the doubtful case. Under any circumstances, however treatment of syphilis in the presence of serological *evidence of its presence is imperative.*

Hysteria.—The tradition of an association of hysteria with syphilis has come down mainly through the French school in the writings of Charcot, Gilles de la Tourette, and Fournier. Whether or not true syphilitic hysteria exists cannot be stated with positiveness. In order to demonstrate the existence of such condition there should be evidence that the hysteria followed instead of preceded the syphilis, and that it responded to treatment for the disease. The variability of hysteria in its successive clinical outbreaks in given individual nearly parallels that of neurosyphilis. Southard and Solomon describe case in which recurrent dazed state suggested hysteric fugues, and this possibility should be by no means lost sight of where clinical signs of neurosyphilis are lacking or are confined mainly to sensory disturbance. The stigmata of hysteria (anesthesia of the conjunctiva, pharynx, nipples, etc., with hyperesthetic zones) are suggestive but not absolutely conclusive. The occurrence of opisthotonos in hysteric seizures (major type) may differentiate the convulsions at sight from those of noisy delirium in cerebral syphilis (Southard and Solomon, Case 67).

Nonne emphasizes the possibility of confusing the transient pareses of cerebral and spinal cord syphilis with hysteric paralyses. In some cases the serological finding may be the chief differential factor. In all doubtful cases spinal fluid examination is in order.

We have occasionally been impressed with the fact that extremely intensive treatment of syphilis, especially with arsphenamine, in predisposed subjects may bring on overtreatment syndrome" (described on p. 372), group of symptoms superficially suggesting a minor form of hysteria. The objective signs of hysteria are however, absent. Reassurance and a rest period usually clarify the situation. Nonne mentions a type of hysteria which he observed in a strenuous therapeutic test of an hysteric individual with supposed neurosyphilis.

Neurasthenia.—The differentiation of neurasthenia and simple nervous states assumes the greatest importance as an issue in preventive medicine, for not only is large part of the symptomatology of early and latent neurosyphilis classifiable under this head, but ith the improved therapeutic outlook of general paresis the period of preparetic neurasthenia becomes the ideal one in which to treat this form of the disease. Accordingly in any patient with even a suspicion of syphilis in his history a blood serologic test is essential and, in view of the numerous instances in which it is negative the properly performed spinal fluid examination may be urged. It should not be forgotten, however that the frankest statement of the necessity for the test and the possibilities of reaction is important in neurasthenic patients in order t prevent the occasional addition of traumatic neurosis ("punctured" spine) to true neurasthenic syndrome. True cerebral neurasthenia in syphilis is often the consequence of psychic shock and anxiety and must be carefully differentiated from the onset of true neurosyphilitic symptoms. Southard and Solomon give a very clear-cut picture of this differential problem (Case 9). After emphasizing the serological criteria they place next in order of importance pupillary and aphasic symptoms. Kraepelin remarks that the sudden occurrence of neurasthenic disorders in a male of middle age, without any evident cause therefor is always suspicious. Yet occasionally dizziness, slight speech defect, tremor of the tongue, and moderate increase of tendon reflexes do not possess any marked significance and may be produced by f tigue and tension. Clear insight and understanding of the nature of the disease phenomena, persistent search for recovery reasonableness in conversation, progressive improvement under appropriate treatment, speak for neurasthenia. Joffroy and Mignot state that the pure neurotic suffers great deal more than the patient who is destined to become a victim of paresis. The character change in neurasthenia does not amount to that entire transformation of personality (even to the performance of criminal acts) that we find in paretic neurosyphilis at the most the neurasthenic shows minor emotional disturbances and a certain pathologic egoism. Psychotherapy readily relieves the true neurotic of many of his fears and feelings. The sexual anesthesia of the preparetic is often preceded by stage of sexual overexcitement. (This may occur in true neurasthenia.) The finer clinical distinctions fade into insignificance beside the results obtained from laboratory tests.

Syphilophobia (previously described).—We have already emphasized in discussing treatment the unwisdom of treating too lightly the so-called "syphilophobic state in patient with undoubted syphilis. Such syphilophobias have too often in our experience been proved, after examination of the spinal fluid, to arise from true neurosyphilis, although the physician had already assured the patient, on the finding of a persistently negative blood serologic reaction, that his fears were imaginary The therapeutic test which acts with such extraordinary promptness in true syphilitic neurasthenia should not be begun without adequate evidence that the symptom complex is of syphilitic origin, for a syphilophobic responds with the greatest alacrity to the suggestive effect of a therapeutic test. The necessity for therapeutic test has largely disappeared with the improvement of laboratory diagnosis.

Encephalitis.—Some reference has already been made to the differential diagnosis of various forms of encephalitis. The lethargic type, with its prolonged course and extraordinary variety of symptoms, has become especially familiar since the influenza epidemic of 1917 18. The differentiation of lethargic encephalitis from syphilis depends almost exclusively upon laboratory criteria and the finding of collateral evidence of syphilitic infection. In the acute phase the pupillary abnormalities and paralyses of extra-ocular muscles which occur accompanied by stupor and paralytic lesions may be indistinguishable from those which may occur in syphilis. In the chronic phase the alterations of personality may simulate the irritable or depressed phases and conduct slump of paretic and nonparetic neurosyphilis. The spastic phenomena which develop later are perhaps more distinctive of lethargic encephalitis than any other feature of the clinical picture yet even these may be simulated in syphilis. In practice one is therefore obliged to rely upon the history and collateral evidence of syphilis and most of all upon the W sserman reaction on the blood and spinal fluid. False positive Wassermanns t least, undoubtedly occur. Other changes in the fluid are not distinctive unless it may be the increased sugar content in lethargic encephalitis. That the therapeutic test must be used with caution is illustrated by the rapid recovery of an undoubted case of early lethargic encephalitis which one of us (J H S) had the opportunity to treat with mercury succinimide. Remission and recovery may however.

be spontaneous. The parkinsonian syndrome may occasionally show slight improvement under arsphenamine therapy but not enough to be deceptive. The presence of a sugar content in the spinal fluid exceeding 80 mg. per 100 cc. is suggestive of lethargic encephalitis, although moderate increase is sometimes seen in neurosyphilis.

The differential problems presented by acute syphilitic encephalitis have been discussed in the description of the condition. A very vivid picture of the maniacal excitement of such patient is given in Southard and Solomon (Case 100). The more acute type may sink t once into stupor and somnolence suggesting encephalitis.

Lead encephalopathy must at times be distinguished from syphilitic encephalitis and the dementias of diffuse cerebral syphilis. Now that bismuth is coming into prominence in treatment, the occurrence of lead (e. g. bismuth) line in the gums cannot be given quite the previous diagnostic weight. The history blood picture and finding of lead in the urine are essential. Very interesting examples of the dementias and convulsive symptoms induced by lead have recently been afforded by the appearance of tetra-ethyl-lead poisoning as an industrial hazard. In the more chronic types lead neuritis with wrist-drop and foot-drop assist in the differentiation.

Uremia.—The differentiation of uremic headache, vomiting, epileptiform convulsions, and coma from neurosyphilis may at times be extremely difficult, especially if they appear in patient previously known to have neurosyphilis. The determination of the blood urea and the blood serologic and spinal fluid findings may be the turning points in diagnosis if the urinary abnormalities and other signs of nephritis are not pronounced. Examination of the fundus of the eye may disclose nephritic retinitis with characteristic hemorrhages. In retinal changes and visual damage as residues of hypertension (renal) and pregnancy intoxication in women who have syphilis, confusion may arise and unnecessary treatment be given.

Epilepsy.—Much of the current discussion of epileptic syndromes in syphilis bears evidence of an unformed opinion and highly theoretic approach. Jacksonian epilepsies present no features distinctive of syphilis and must be identified as such on serological and collateral clinical evidence. True epilepsy and generalized syphilitic epileptiform convulsions are likewise clinically indistinguishable in some cases. If following an apparently true epileptic convulsion, aphasia and pupillary abnormalities, cranial nerve, and other paralyses are found, syphilis is suggested and true epilepsy eliminated. It is apparently possible for true epilepsy to recur as manifestation of syphilis for many years (parasyphilitic epilepsy of Fournier) without any distinguishing signs. Nonne notes, however that the intelligence suffers much less in these cases than in true epilepsy and that long remissions and onset very late in the course of the disease are quite characteristic. The true epileptic seizure maintains more constant character over period of years than does that of neurosyphilis. Petit mal seizures may appear during intervals of seeming quiescence. Petit mal seizures may likewise appear in the course of cerebrospinal syphilis and after apparently effective treatment in paresis (especially juvenile) without major attacks and persist over period of years unaffected by treatment and without substantial change. Such symptoms may perhaps be the effect of microscopical healing in the brain. Serologically negative, but none the less syphilitic, epilepsy occurs and can sometimes be recognized by therapeutic test. It is, however decidedly rare and does not justify the wholesale application of such test to cases of apparently typical idiopathic epilepsy without satisfactory collateral evidence of syphilis.

Migraine.—Recurrent headaches in neurosyphilis may be interpreted as migraine, and *vice versa*, especially if accompanied by vomiting. The familial history of periodic headache and allergic background, the unilateral character in the typical case, and recurrence of the ttacks at regular intervals over period of years suffice for differentiating typical cases. On the other hand, the distinction is not always so easily drawn. In severe migraine accompanied by ophthalmoplegia, only full serological and clinical examination may eliminate syphilis. Stokes has personally observed patient in whom the severity of the gastro-intestinal phase of the migrainous attack and the mildness of the headache had led to mistaken diagnosis of gastric crises. In the severe cases, accompanying headache, blindness, aphasia, in the attack, and the family history assist in differentiation. Wolfman mentions women with both tabetic crises and abdominal migraine.

Diabetic Syndromes.—Polyuria, polydipsia, and occasionally glycosuria may lead to the ascribing of diabetic origin to neurosyphilitic cerebral and basilar meningeal disturbances. Lesions in the chiasm produce, according to Nonne, the characteristic sequence of basilar cranial nerve paralysis, polydipsia, and hemianopsia, with or without hemiplegia. x-Ray examination of the skull may show deepening of the sella turcica or changes in the clinoid processes which may be gummatous in origin. Diabetic pseudoparesis may suggest general paresis in its onset, and the differentiation only be made by serological findings. Pupillary abnormalities are rare in diabetes, but when they occur in association with peripheral neuritis they produce the picture of diabetic pseudotabes with loss of reflexes and lightning (neuritic) pains. The neuritis of diabetes is es-

sentially polyneuritis, and involvement of other nerves with polyneuritic atrophic changes and absence of evidence for syphilis must be the diagnostic resorts. The occurrence of a *false positive* blood serologic reaction in diabetes can, in the light of recent investigations, be practically dismissed in differential study.

Multiple Sclerosis.—*This differentiation,* constituting in many respects the most difficult confronting the neurosyphilologist in the pre-Wassermann era, has been greatly simplified by spinal fluid examination. Syphilis may produce multiple areas of sclerosis in the nervous system; and similarly suitably placed sclerotic changes in multiple sclerosis may give rise to pictures indistinguishable from neurosyphilis. The *familiar* earmarks of multiple sclerosis, including nystagmus, optic nerve atrophy, intention tremor, and scanning speech, are not by any means invariably present and more confusing symptoms such as ocular muscle palsies, hemiplegic attacks, bladder disturbances, and spastic paraplegia may make clinical *differentiation* difficult or impossible. Mental changes have been shown to occur in multiple sclerosis, and mental confusion, maniacal states, and grandiose delusions are recognized. Sclerosis of the posterior spinal roots may give rise to lightning pains. Nonne has observed the Brown-Séquard syndrome in multiple sclerosis.

Furthermore, some cases of multiple sclerosis respond definitely to treatment for syphilis, especially with the arsphenamines, although spontaneous remission must be thought of. The effect is by no means so great as in neurosyphilis of a similar clinical type. *In fact,* marked delay and small returns in a therapeutic test for an atypical neurosyphilitic syndrome with negative spinal fluid Wassermann should, *if other evidence for syphilis is scanty,* arouse some suspicion of multiple sclerosis.

The characteristic spinal fluid findings of the two conditions are usually sufficient to make the diagnosis. In multiple sclerosis the spinal fluid Wassermann is negative even to large amounts; there is rarely any increase in globulin, but there may be pleocytosis, usually slight. The first zone or paretic curve is present in perhaps 40 per cent. This combination of paretic curve with negative blood and spinal fluid Wassermann rarely fails to establish or confirm the diagnosis.

Infectious Cerebrospinal Meningitis.—The differentiation of acute infectious cerebrospinal meningitis, whether due to the meningococcus or streptococcus, calls for culture and microscopical examination of smears from the spinal fluid sediment. This should be done routinely in connection with all spinal punctures in acute disease of the nervous system. The occurrence of fever, leukocytosis, and of polymorphonuclear cells in the cytological examination cannot be accepted as diagnostic, for they may occur in syphilis. The *identification* of a *focus* of infection, such as mastoiditis, is, of course, contributory *evidence.* In all cases of doubt it is wiser to give antimeningitic serum coincidentally with the diagnostic spinal puncture than to postpone it until the results of bacteriological examination are received. This precaution we learned from several cases in which a delay due to overcaution seemed responsible for the unfavorable result. Blood culture sometimes contributes to the identification of a nonspecific infectious factor where the patient is known or suspected to have syphilis. Southard and Solomon cite a case of taboparetic neurosyphilis in which the terminal picture was that of typhoid meningitis without other clinical symptoms of typhoid fever.

Tuberculous and Other Forms of Meningitis.—The differential diagnostic problem arises more frequently in tuberculous than in more acute *forms* of meningitis. The diagnosis frequently depends upon the serologic negativity of the blood and spinal fluid and the finding of tubercle bacilli on microscopical examination of the spinal fluid sediment and guinea-pig inoculation. Weak positive serologic reactions sometimes appear in the spinal fluid as in other meningitides. The formation of a clot in association with a low sugar (18 to 40 mg.) and chloride content is practically diagnostic of tuberculous meningitis. Localized tuberculous meningo-encephalitis may, according to Nonne, produce symptoms indistinguishable from those of gummatous meningitis. The general habitus of the case and the serologic reaction on blood and spinal fluid, which may, however, sometimes be negative, must be relied upon to distinguish these cases. In solitary tubercle of the pons the symptoms may simulate those of syphilitic thrombosis of the basilar arteries or gumma, or focal syphilitic meningitis as described by Southard and Solomon (Case 6).

Cysticercus and actinomycotic meningitis are identified by the spinal fluid findings. Tularemic meningitis (recall tularemic "chancre"), torulosis (Stiles and Curtiss, 1931) and blastomycosis must be kept in mind.

Cord Tumor.—The differential diagnosis of spinal cord tumor is growing in importance. Since syphilitic meningeal gummatous involvement can produce symptoms indistinguishable from cord tumor, it is obvious that there must be some cases in which the diagnosis will depend entirely on laboratory findings and collateral clinical evidence. In old fibrous sclerotic gummas all criteria may fail and the nature of the process be discovered only at operation. Gummatous

invasion of the cord itself (localized gummatous myelitis) may likewise produce symptoms of cord tumor The serologic reaction is practically the only distinctive differential criterion in these cases. There is nothing distinctive in the cellular content, and the compression syndrome with xanthochromia may appear in a cord tumor of syphilitic origin precisely as under other circumstances.

Cerebral Symptoms and Cord Changes of Pernicious Anemia.—The patient with primary anemia of the addisonian type may exhibit mental symptoms (Woltman) of the infection-exhaustion type, or alterations of personality The former may include delirium, delusion, hallucination, paranoid states, and dementia, the latter ranges from mild indifference or abnormal affability and gentleness to shallow confusion, torpor and dream states. The most distinctive objective early sign of the cord changes, according to Woltman, is from the posterior columns as in tabes, and includes loss of vibratory sense and sense of motion and position. Pain, tactile and temperature sense are preserved almost intact. Knee jerks may be lost if the posterior columns are affected and a positive Babinski test may indicate the changes in the lateral columns. The patients suffer from paresthesias, numbness, prickling and "silk-glove" sensations, but rarely have pains, which assists in distinguishing the picture from serologically negative tabes, in which pains are often present. Optic atrophy and the Argyll Robertson pupil accompany tabes, but not primary anemia, while retinitis of the anemic type is a very common feature of primary anemia (90 per cent) The differentiation is not difficult if the blood and spinal fluid are positive, but in those patients in whom cord changes appear before the blood picture of addisonian anemia is clearly defined, or during a blood remission, as well as those in whom a false positive blood Wassermann reaction may be present, the differentiation may momentarily present something of a problem. Patients with tabes rarely develop a degree or type of anemia which is likely to be regarded as primary The completion of the case, as a whole, here as in other differential problems, is the only safe guide. The response of primary anemia to arsphenamine should not be forgotten in attempting a therapeutic test.

THE TREATMENT OF NEUROSYPHILIS

The Recent Changes.—As one surveys the field of the treatment of neurosyphilis during recent years, one observes, as in the field of cardiovascular syphilis, a gratifying trend toward more rational and better-grounded interpretation and toward the conquest of the more resistant manifestations.

What might be called localizing or topical methods of attacking syphilis of the nervous system as, for example, intraspinal and intraventricular therapy are losing ground with the advent of three notable advances: (*a*) the more thoroughgoing and systematic systemic treatment of early syphilis; (*b*) the use of drugs with high penetrating power for the nervous system, particularly pentavalent arsenicals; (*c*) the employment of nonspecific stimulation of the defence mechanism, including fever and nonspecific protein therapy

The Objectives of Treatment.—The first aim of treatment in neurosyphilis is to restore a sick man to effectiveness, to make him act and feel better It is not, of course, to reverse a serological reaction or even to reduce a single symptom to absolute zero at the cost of physical collapse or economic ruin for the rest of the man. In the evaluation of treatment results the restoration of economic status and the replacement of the disabled individual in the niche in the social scheme which he occupied before the disease produced its destructive effects, is assuming increasing importance both as a fact and as a method of mensuration of treatment effect. It will deserve increasingly critical analysis in the future as we watch the return of treated general paralysis with its dangerous potentialities for individual, family and social life to the community at large. A second aim of treatment is to make the benefit obtained by therapeutic procedure as nearly permanent as possible. Inevitably the evaluations in this field will be a matter of years and decades rather than months, and almost no information as yet available equals or transcends the first ten-year period since the adoption of the most effective

special methods. A third aim, negatively speaking, must be the avoidance of therapeutic hobbies and the employment in the individual case of each and all the methods that may seem, under skilled judgment, to be applicable to the particular problems presented. The fourth aim is an inevitable corollary of the third—the treatment of neurosyphilis in the later years becomes in the highest degree a matter of individualization as contrasted with the essential use of vigorous routine in the earliest years of the infection.

STANDARD OR PRACTITIONERS' METHODS IN THE TREATMENT OF NEUROSYPHILIS

The Prevention of Late Neurosyphilis.—Despite the fact that there still remain unsettled questions in regard to the comparative evolution of untreated and treated asymptomatic neurosyphilis, there is no longer any reasonable doubt of the worth of thoroughgoing treatment of early syphilis in the prevention of late neurosyphilis. The treatment of early syphilis, in this country especially, is a practitioner's problem. There can be therefore no escaping the fact that the prevention of late neurosyphilis is his responsibility. To the extent that he is able to put into effect the standards for early treatment described in Chapter XIV, the consequences of syphilis in the neurological field will disappear from the clinical scene. Inasmuch as we have several times emphasized the large place held by neurosyphilis in the clinical symptomatology of internal medicine with respect to the disease, the real meaning of such a reduction in morbidity and mortality can be imagined.

The preventive management of early neurosyphilis has been reviewed on page 673 and summarized in Fig. 445. The practitioner can be bolstered in his determination to see the issue through in the individual case by the figures summarized below.

Keidel and Moore found that after 12 or less doses of arsphenamine with courses of mercury the spinal fluid showed abnormalities in 21.4 per cent of cases, while after 13 or more doses of arsphenamine with mercury the proportion dropped to 8.7 per cent. The striking effects of energetic early treatment on the prevention of asymptomatic neurosyphilis is again shown in Zurhelle and Krechel's results in Hoffmann's clinic (Fig. 725). The Cooperative Clinical Group, it will be recalled, including tryparsamide and malarial therapy results in their statistics, found that only 6.8 per cent of the abnormal spinal fluids observed in their large series proved irreversible by treatment. Relatively little treatment by modern methods readily reduces slight abnormalities to normal. Marked abnormalities, on the other hand, are less responsive from every standpoint and the presence of a positive Wassermann reaction in the spinal fluid particularly, even though not in conjunction with a typical paretic formula, demands intensification of treatment (see p. 120) and prolongation over at least an additional two years from the time the abnormality is discovered. The later in the course of effective treatment such abnormalities are identified, the more serious they are. The more recent demonstration by Padget (1940) of the prophylactic effect of treatment of early syphilis against the development of neurosyphilis should be recalled. The incidence of neurosyphilis dropped from 11.3 per cent in patients who received 1 to 3 doses of 606 during the first 3 months of treatment to 9.9 per cent after 4 to 6 doses and 7.6 per cent after 7 to 9 doses.

The "red flag" formula or the "paretic" spinal fluid (Type III) is the practitioner's warning of grave danger for his patient. In the Cooperative Clinical Group study this particular formula proved to be at least twice as difficult to reverse to normal as any other markedly abnormal spinal fluid. When such a formula is recognized, therefore, there should be no delay in shifting not only to the intensified methods of standard treatment but to the use of tryparsamide and fever therapy if a prompt response is not secured. It is here precisely that our greatest weakness has lain. If the

spinal fluid was examined at all in the past decade, treatment by routine weekly injections of neoarsphenamine was continued over months and sometimes over years with the gradual decline of the patient and a total lack of significant therapeutic effect.

The importance, from the preventive standpoint, of the institution of treatment at the earliest possible moment in the course of a syphilitic infec-

Fig. 702.

WHEN NEUROSYPHILIS APPEARS AS A COMPLICATION WHETHER ON FIRST OR SUBSEQUENT EXAMINATION OR IN THE COURSE OF TREATMENT

1. There is no occasion for hopelessness or panic. Treatment results are good.
2. Secure base-line physical general and neurological survey for present and future reference (Chapter II).
3. Have fundus, vision and fields examined if possible at once
4. Detect intercurrent disease and identify all forms of syphilitic involvement, especially cardiovascular
5. Consider tolerance for various treatment possibilities, in advance of trouble, not after it.
6 Weigh acuteness and rapid progression signs. Cataclysmic methods may give catastrophic results.
7 Recall the dangers of therapeutic shock and prepare practically all cases with iodide and heavy metal.
8. Remember the patient as whole has syphilis—not just one part of him, and treat him accordingly
9 Value system for the average early case and the young patient, insist on it.
10. Individualize th acute, the late case the "wreck.
11 Never "hammer" the aged, the arrested, the quiescent patient.
12. At each interview look first at th patient; then at his record.
13. Refuse hurry reject stampede, avoid fads, check overenthusiasm, resist routinized thinking, especially in treatment decisions involving methods. A living dog is better than a dead lion.
14 But value youth, resistance, clear-cut early warning of grave dangers ahead (e. g "the red flag syndrome") and strike full force (e. g., malaria) when necessary—no trifling with half measures.
15. In other than paretic and acute or critical localized forms of neurosyphilis, be conservative, persistent, even leisurely—results take eeks, months, years, and involve the whole resistance and constitution of the patient, not merely spirillicides and serological test.
16. Place clinical improvement first among objectives and criteria.
17 Make serological negativity an intelligent treatment aim but not fanatic obsession.
18. Maintain but don't overdo spinal fluid control, only examining the fluid when the next move depends on it, not as mere routine.
19. Value rest—"The boatman reacheth the landing, partly by pulling, partly by letting go.
20. But never prescribe therapeutic inactivity merely from laziness.
21. Let treatment results determine further treatment and prognosis.
22. Have a heart as well as head. Help the patient with the personal problem of his disease.
23. Study the family and examine the marital partner of every neurosyphilitic patient.

tion stood out clearly in the Cooperative Clinical Group investigation and deserves reemphasis here. Irreversibly positive spinal fluids were twice as frequent when treatment was begun in early secondary syphilis (1.3 per cent) as when treatment was begun in seronegative primary syphilis (0.6 per cent).

The General Principles of Treatment of Established Asymptomatic and Symptomatic Neurosyphilis.—All treatment problems in neurosyphilis have

certain elements in common and we have accordingly attempted in Fig 787 to summarize a number of considerations that should apply when neurosyphilis appears or is recognized as a complication in the management of any given case whether the occasion be that of first or subsequent examinations or in the course of treatment.

Between the pessimism of the older generation and the prearsphenamine era and the stampede toward fever therapy the really distinguished merits of systematic routine treatment with the arsenicals, mercury bismuth, and the iodides, are at times in danger of being discounted or overlooked

A medical examination of the patient before treatment is begun should detect evidence of renal insufficiency and disturbance of excretory function, so common especially in old tabetics. The cardiovascular system may present lesions which positively contraindicate massive treatment, at least at the outset. It may present warning of a cardiovascular lesion that may progress after treatment for the neurosyphilis, especially fever is completed. Similarly with the advent of fever therapy the eligibility of the case for this method of treatment should be considered from the start and not after it is found that every other resource has been exhausted without effect. The general principles for the avoidance of complications are often especially important in late neurosyphilitics. The examination of the eye (item 4) should be undertaken before arsphenamine is begun, to detect warnings of impending primary optic atrophy including pallor of the disks to detect damage done by the disease before treatment is instituted as a matter of medicolegal as well as purely medical protection and to assist in deciding whether tryparsamide may be counted among the eligible procedures. The detection of intercurrent disease is extremely important and death from diabetes (Osborne) and from the activation of tuberculosis, or the complications of pregnancy has occurred from neglect of this consideration. Acuteness and [illegible] of rapid progression of a process in the central nervous system demand an adequate preparation, though the technic need not be robbed of effectiveness by this consideration. As our personal experience with the unexpected increased, our caution in the matter has grown [illegible]. Even though the infection does not seem extremely active, we now believe that practically all patients should receive preparatory treatment, before the institution of arsphenamine or special treatment methods. After all, many patients with seemingly active and even symptomatically grave neurosyphilis, to say nothing of paper syphilis, have lived effective and not-too-troubled lives on minimal treatment or even no treatment at all. A lengthening experience tends to temper therapeutic furore In the baseline neurological summary special attention should be paid to items which may show improvement under treatment, including the size and distribution of the areas of sensory change and subjective symptoms such as paresthesia, pain, visual disturbance and so forth. Focal infection, especially in the patient with many subjective complaints and much debility deserves careful study and may be the clue to an entire situation that obstinately refuses to yield to therapeutic bombardment. The tonsils and teeth, the sinuses, the gallbladder, and appendix less often, the colon more often, the bladder and prostate and the uterine cervix may be contributing to the exaggeration of the clinical picture, as we have indicated in the general discussion of treatment.

Value and Use of System.—Average neurosyphilis, if the fundamentals of protection from explosive reaction at the outset, avoidance of toxic complications and positive contraindications be kept in mind stands routinization well and "system greatly promotes the confidence of the patient in his treatment and his ability to adjust himself to the demands of a thorough-going cure. If the patient is told at the outset that eight or ten weeks of concentrated treatment, then four months of virtual self-treatment and rest will be followed by a similar course three to five times in succession, he makes arrangements inspired by the definiteness of his outlook which in our experience are better adhered to than those which follow a vague statement that treatment may continue an indefinite period. The patient must of course be told that decisions are modifiable by the course of his case but it is better here as elsewhere to plan a maximum rather than a minimum

Many times patients have expressed to us their personal appreciation of organization in method and definiteness in program as factors in their rehabilitation. On the other hand, worship of system by the physician himself if it blinds him t the fact that given case has achieved the best possible result in less than regulation time, is misguided, and ultimately damages the patient cause.

Acute and Very Late Cases Individualized.—The acute case and the very late case call for those indefinable juggleries of method which only experience can suggest. An acute case in general is marked by a high spinal fluid cell count, objective evidence of an acute process, as an encephalitis or myelitis, a rapid advance of symptoms, such as pains, bladder disturbance, ataxia, failing vision, palsies of cranial nerves, cerebral accidents, and choked disk. For the large majority of such cases we have found nothing superior as preparation to the soluble mercurial salt intramuscularly provided the patient is not greatly emaciated. The severely debilitated patient may do better on inunctions. The best effects of medication by mouth, and, in fact, almost the only field for it is in the late case in which a gain in weight is especially desired.

Therapeutic Shock (Herxheimer).—The therapeutic shock is as real in all types of even moderately intensive treatment for neurosyphilis as in early secondary eruptions (see Chapter VII) The clinical increase in symptoms during the first few weeks is something of which the patient may well be warned and which may be interpreted to him as a favorable rather than an unfavorable sign. In patients exhibiting mental symptoms it must be provided for in advance, lest an attempt at suicide or an act of violence terminate the case Genuinely unfavorable progress of a patient and a merely transient Herxheimer reaction may be confused In general, we have found the less significant Herxheimer reaction to affect subjective sensory disturbances, while the more serious symptoms of unfavorable progress include the objective signs of increasing ataxia, bladder paresis, and vascular accidents or convulsions. Numbness of the extremities has, however sometimes appeared as a subjective sign of genuinely unfavorable progress.

Discipline and Cooperation.—Among the general principles of management we consider it mark of the experienced therapist to refuse to be hurried, and to maintain discipline in his patient' case, so to speak, by insisting on adherence to regimen devoid of uncalled-for temperamental variations. The patient who will not keep treatment appointments, refuses reasonable checks upon his condition, and insists on relying solely on his feelings and business convenience, as in all aspects of the disease, is sometimes unpredictably successful in escaping consequences, but is usually the first to blame the physician for an unfavorable turn of affairs. For this reason it is important to appraise the patient from this standpoint at the first interview if possible. There is, however certain amount of adjustment of the patient treatment to his personal situation which should be made in all possible cases. The less it galls him, the better his response and the better adjusted t his economic situation, the longer he will continue it; point of much significance in the late neurosyphilitic whose means have often been spent in futile search for health, and whose earning capacity t best is below par

Help with Personal Problems.—Helping the patient with the personal problems consists first in determined reassurance wherever such is even faintly justifiable. The response of the neurosyphilitic to reassurance sometimes surpasses the effect of antispecific medication if it comes from a trusted and experienced source and as the result of a full consideration of the case. Neurosyphilis so often comes as a complete surprise that adjustment of family relations and the informing of the marital partner (see Chapter XXI) are essential to clear the way for really effective treatment.

Indefinable Personal Impressions of the Patient.—The injunction to look at the patient first and his record later seems trite, but is a real problem of the busy consultant and practitioner. The asymmetry of the face in a beginning hemiparesis, the "flabby" expression, the changes in speech, in gait, in consciousness and insight, in weight, complexion, lustre of hair, color of sclerae, and even the identification of the faint odor of urine, all at times outrank in importance anything to be found in the laboratory reports. "He doesn't look good" is sometimes the only justification, but a perfectly proper one for a change of methods.

The Value of Rest.—There can be no doubt that there is a very close relation between the recuperative or rest period and the "cure" of the case. The effect of treatment on neurosyphilis is slow, comparatively speaking, and cumulative, so that it may not be until weeks or months have elapsed and during a period of suspension of treatment that the patient begins to rally to the physician's satisfaction and his own.

A definite reduction in the scale of energy output of intense personalities is desirable, yet complete inhibition of their activity may throw them into a depression and introspection whose effects are worse than those of overtreatment. An excellent practical device for the busy patient is the breaking of the day in the middle by an hour['s] rest with a nap, a scheme which is life-saving in many aspects of medicine. The "fishing trip," if of the Izaak Walton or the "dry" type, has come to be a familiar phrase for the recuperative period.

Examination of Conjugal Partner.—The frequency of conjugal neurosyphilis is such that every marital or sexual partner of a neurosyphilitic is suspect, and should have a full study if possible, including a spinal fluid examination when the spouse was married within the infectious period of the patient's disease. It is theoretically desirable perhaps to make the rule invariable for all cases, but we rarely urge it if marriage took place later than ten years after infection and there are no collateral confirming or suspicious signs. The children of every neurosyphilitic patient should be clinically examined, and those who show signs of syphilis should have spinal fluid examinations in addition to the usual tests.

The Standard Drugs in Neurosyphilis: the Arsenicals.—Arsphenamine (606) has the right to priority on the score of its general greater therapeutic effectiveness. It is proper to say, however, that much Continental practice, particularly in France, has centered around the use of neoarsphenamine in the treatment of neurosyphilis by technics employing small dosage and frequent injection with apparently satisfactory results in all but the specially refractory conditions. The problem of treating symptomatic neurosyphilis other than paresis is not in general one of overwhelming the disease with an enormous mass of treatment. For this reason we have incorporated in the unit courses of technic two very serviceable plans, one relatively intensive and one tonic, which exhibit the general principle of shortened intervals, longer courses, and a closer amalgamation with the heavy-metal phase which is now known to increase the effectiveness of neoarsphenamine therapy. Sicard has reported excellent results in tabes dorsalis from the intramuscular use of neoarsphenamine in long series beginning with minute doses.

The Arsenoxides (Mapharsen, Dichlorophenarsine).—While not yet clearly evaluated in neurosyphilis, there is a disposition to replace the arsphenamines by the arsenoxides that cannot be gainsaid. If this is done they

should be given not less than twice weekly or for maximum effect 3 times weekly in doses of 60 mg or more per injection for from eight to twelve weeks, with bismuth concomitantly (subsalicylate, weekly) somewhat as in the Eagle-Hogan intensified technic for early syphilis (Chapter XIV)

Bismarsen is useful as tonic or mild type of treatment and secures reversals of the less serious spinal fluid changes in 60 per cent of cases in series of 40 injections or more. It has good symptomatic effect on tabetic pains and meningeal headaches in debilitated patients.

Bismuth is notably effective in securing the relief of subjective symptoms in tabetic neurosyphilis. It is therefore an essential element in all treatment schemes and with the development of better penetrating compounds will probably assume an increasingly important rôle. The iodobismuthite (Iodobismutol) despite controversy on its penetrating powers is an effective and useful drug if its technic of administration is mastered In patients subject to risk of complications from the use of arsenical bismuth is particularly valuable and well tolerated

The mercurials in neurosyphilis deserve a higher place than the growing ascendancy and popularity of bismuth will probably allow them. Recent experimental work tends in an interesting way to explain the genuine and deserved popularity of the massive mercurial inunction in the long-run treatment of neurosyphilis, as for instance by the Aachen technic. Hoff found that in dogs it was possible to demonstrate mercury in the central nervous system, usually within eight hours following mercurial inunction, though following the succinimide the results were less definitive or negative. He found also that large doses of iodide hastened excretion of mercury but small doses apparently delayed excretion in dogs. To mercury therefore we would assign an important place in the treatment of neurosyphilis as in the unit courses of Fig 763 where mercury by inunction is a major interim feature of one of the systems. From a long experience both with the soluble mercurial salt (succinimide) and the massive mercurial inunction, we feel that they are as yet irreplaceable in the determined assault upon an intrenched neurosyphilitic process other than paresis. It is our impression that the intramuscular use of a mercurial in conjunction with tryparsamide materially increases the effectiveness of that arsenical likewise, this being a feature of the Lorenz Loevenhart technic.

Iodide in neurosyphilis occupies an undoubtedly important but not technically well-defined position. W have based our interpretations on Osborne observations. The enormous increase in iodine content of the spinal fluid by the use of sodium iodide intravenously while brief and often conditioned by meningeal involvement has genuine therapeutic merits. The intravenous use of sodium iodide is not, however advocated particularly for the elderly quiescent case, liberal doses by mouth being preferred. The use of sodium iodide intravenously alone is sometimes an excellent preparatory treatment and occasionally gives quite striking results, but combination with heavy metal and particularly with mercury rather than bismuth is preferred. A preliminary trial of iodide by mouth, to test tolerance, is essential for patients who are to receive iodides intravenously

Stampede and Fadism *versus* Overconservative Delay —Much of the wisdom accumulated by prolonged experience tends inevitably toward conservatism. One learns, and not alone through progressive senile endocrine

deficiency or arteriosclerotic change in himself the singular virtue in many situations of doing relatively little of avoiding strenuosity and of invoking the resolving power of time in a genuinely masterly inactivity Aphoristically stated, we may fall back upon Ochsner's famous dictum "Leave something to God" and accept a partial result in a living patient as preferable to an attempted cure with a fatal outcome, on the principle that a living dog is better than a dead lion. Thus, one will sometimes mistakenly but often wisely withhold malaria in a conservative interpretation of a situation in late neurosyphilis. On the other hand a routine or pigheaded conservatism is an abomination and a consistent setback to progress. As rapidly as clear cut good results *justify the taking of special risks or as the margin of special risk* is reduced by extending experience promptitude in radical or intensive methods becomes more important even than the methods themselves. Thus, in the early utilization of the advantages and assumption of the risks of malarial therapy while a relatively unimpaired (asymptomatic) nervous system and good physical resources in the patient give us every advantage,

Fig. 703.

UNIT COURSES OF STANDARD TREATMENT IN NEUROSYPHILIS
PREPARATORY UNIT (1 and 2 are alternatives.)

1 Mercury and iodide.
   (a) Hg succinimide or bichloride intramuscularly ⅙ to ¼ grain, three to five times a week for 20 to 30 injections.
   (b) Potassium iodide by mouth, 50 to 100 grains three times a day
2. Bismuth intramuscularly (water-soluble sodium tartrate liposoluble camphocarboxylate, salicylate iodobismuthate) once to three times weekly depending on the salt, for 10 (insoluble) to 20 (soluble) injections.

Discussion

(a) The mercury-iodide preparatory unit is preferred in very acute or rapidly advancing lesions, or in the presence of vascular or visceral complications.
(b) A mercurial or bismuth unit may be used simultaneously with, in preparation for or as interim treatment between arsphenamine or neoarsphenamine courses.
(c) The iodide may be used with the bismuth, or an iodobismuth salt employed.
(d) A mouth prophylaxis and preliminary iodine tolerance test are necessary

is a demand of rather than a concession to progress. The young preparetic recognized as such by his spinal fluid findings or by the earliest symptoms of the disorder is the candidate *par excellence* for the life-saving virtues of malarial therapy

Standard Treatment. —By this term is meant conventional arsenical and heavy metal therapy as outlined for example in Fig. 704. The question as to whether standard treatment est right wast time hen neurosyphilis with type III (preparetic) spinal fluid is recognized, is not fully resolved. It is conservative, and we do not believe it wastes time to give the unit course of Fig 704 if there are no urgent or deteriorative symptoms, and the patient has had no previous standard treatment Each case must be decided on its merits.

The "Unit Course. —In Figs. 703 and 704 are outlined several preparatory and several arsenical-heavy metal unit courses which may be conceived as constituting the building blocks from which a standard treatment regimen may be built up. While such a group of seemingly standardized procedures may appear to fly in the face of the proposed individualization,

such is not in reality the case. The use of treatment units will give to the management of the large majority of patients the touch of system whose value has already been emphasized. Some of the combinations are suggested in discussion of the outlines.

A Scheme for Treatment in Neurosyphilis.—While the individual specially difficult and particularly late case may require consultant assistance in individualization, it is possible to summarize current trends of reasonable but not ultraconservative practice in the treatment of neurosyphilis in a way

Fig. 764.

UNIT COURSES OF STANDARD TREATMENT IN NEUROSYPHILIS

Arsphenamine-Heavy Metal Unit.

(1, 2, and 3 are alternative types.)

1. Arsphenamine 606 intravenously preferred in uncomplicated cases; 6 to 10 injections, 0.3 to 0.5 Gm. each, weekly intervals, followed by bismuth intramuscularly (salicylate, liposoluble camphocarboxylate, iodobismuthite) in full adult dosage for 8 to 10 injections.
   (a) Arsphenamine 606 intravenously with coincident mercury succinimide or bichloride as in preparatory unit (Fig. 765)
   (b) Arsphenamine 606 intravenously 6 to 10 injections followed by 40 single or double (4 or 8 Gm.) 50 per cent mercurial inunctions (5 or 6 each week) and one month rest.
2. Neoarsphenamine 914 intravenously 0.45 to 0.6 Gm. every three to five days for 10 to 14 injections with ½ dose of bismuth (see No. 1) coincidently intramuscularly for 20 injections, the bismuth being continued beyond the neoarsphenamine course with full adult doses when given alone.
3. Neoarsphenamine "tonic (nonintensive) unit"; 8 to 12 intravenous injections beginning 0.15, 0.3, 0.45, and 0.45 or 0.6 Gm., etc., weekly alternating with (a) mercury succinimide unit or (b) 20 injections of iodobismitol twice weekly
4. Mapharsen or equivalent arsenoxide, 20 to 25 injections 2 or 3 a week, 60 mg. average dose per injection, with weekly injections (8 to 10) of bismuth subsalicylate 0.2 Gm. per injection.

Discussion

(a) The arsenical together with the heavy metal which follows or is given with it, constitutes the unit.
(b) Units may be combined into alternating continuous treatment or rest periods may be allowed after the heavy-metal part of a unit, but not after an arsenical.
(c) When mercury is employed, rest periods are more necessary
(d) The tonic unit is appropriate only to late and badly debilitated cases.
(e) Neoarsphenamine is preferred if there are coincident cardiovascular lesions.

that has been attempted in Fig. 765 It will be noted that practically every type of case is subjected to preparatory treatment, even to the advanced and deteriorated paretic who is given preparatory treatment for the purpose of appraising his treatment tolerance before putting him to the life-and death test of malarial or even tryparsamide therapy The necessity or desirability of preparatory treatment as a preliminary to malarial therapy has been emphasized by Jacobs and Vohwinkel, Kerl Mulzer Jadassohn O Leary and Osborne. In the use of routine or unit courses it must be emphasized that the arsphenamine and the heavy metal are indispensable to each other and that the course should terminate with a heavy metal. Overlapping, or staggered, intermittent, and continuous systems may be compounded of

deficiency or arteriosclerotic change in himself the singular virtue in many situations of doing relatively little, of avoiding strenuosity and of invoking the resolving power of time in a genuinely masterly inactivity Aphoristically stated we may fall back upon Ochsner's famous dictum "Leave something to God and accept a partial result in a living patient as preferable to an attempted cure with a fatal outcome, on the principle that a living dog is better than a dead lion Thus, one will sometimes mistakenly but often wisely withhold malaria in a conservative interpretation of a situation in late neurosyphilis. On the other hand a routine or pigheaded conservatism is an abomination and a consistent setback to progress. As rapidly as clear cut good results justify the taking of special risks or as the margin of special risk is reduced by extending experience, promptitude in radical or intensive methods becomes more important even than the methods themselves. Thus, in the early utilization of the advantages and assumption of the risks of malarial therapy while a relatively unimpaired (asymptomatic) nervous system and good physical resources in the patient give us every advantage,

Fig. 703

UNIT COURSES OF STANDARD TREATMENT IN NEUROSYPHILIS PREPARATORY UNIT (1 and 2 are alternatives.)

1 **Mercury and iodide.**
   ( ) Hg succinimide or bichloride intramuscularly ⅙ to ⅕ grain, three to five times week for 20 to 30 injections.
   (*b*) Potassium iodide by mouth, 30 to 100 grains three times a day
2. Bismuth intramuscularly (water-soluble sodium tartrate lipsoluble camphocarboxylate, salicylate iodobismuthite) once to three times weekly depending on the salt, for 12 (insoluble) to 20 (soluble) injections.

Discussion

( ) *The mercury-iodide preparatory unit is preferred in very acute or rapidly advancing* lesions, or in the presence of vascular or visceral complications.
(*b*) A mercurial or bismuth unit may be used simultaneously ith, in preparation for or as interim treatment between arsphenamine or neoarsphenamine courses.
) Th iodides may be used with the bismuth, or an iodobismuth salt employed.
(*d*) A mouth prophylaxis and preliminary iodin tolerance test are necessary

is a demand of rather than a concession to progress. The young preparetic recognized as such by his spinal fluid findings or by the earliest symptoms of the disorder is the candidate *par excellence* for the life-saving virtues of malarial therapy

Standard T eatment —*By this term is* meant conventional arsenical and heavy metal therapy as outlined for example in Fig. 704. The question as to hether standard treatment set right extra time when neurosyphilis with type III (preparetic) spinal fluid is recognized, is not fully resolved It is conservative and we do not believe it wastes time to give the unit course of Fig 61 I there are no urgent or deteriorative symptoms, and the patient has had no previous "standard treatment. *Each case must be decided on its merits.*

The 'Unit Course "—In Figs 703 and 704 are outlined several preparatory and several arsenical heavy metal unit courses which may be conceived as con tituting the building blocks from which a standard treatment regimen may be built up. While such a group of seemingly standardized procedures may appear to fly in the face of the proposed individualization,

sultation, for the protection both of physician and patient, precisely as in decisions involving major operations. In preparation for such decisions, adequate serological data are indispensable and are more often used in final judgment than the mere evidence of clinical improvement, though the latter is the ultimate at least at the present day of a favorable outcome. Good and complete tests on the spinal fluid are especially important. In a patient who has been for some time under routine measures without adequate serological response, a physical and neurological reappraisal as well as merely paper findings will be essential to a decision. The impressions of the family and particularly of the wife or husband on subtle changes, such as nocturnal petit mal attacks, altered disposition and "conduct slump," may be very important. A general enthusiasm for a method should never be substituted for the most painstaking consideration of specific indications and contraindi cations in each and every case

Value of Prolonged Treatment.—In summarizing the schemes applicable to the various types of neurosyphilis where reliance is placed largely on unit courses of standard treatment, emphasis should be on the prolongation of the treatment until a result is achieved In the subsequently reported results of standard treatment obtained by Shaffer and Stokes the average number of courses approximating the unit type with or without intraspinal therapy required to produce the results presented was three three to five courses are therefore made the average expectancy Only 30 per cent of our cases required four or more courses. The question as to how long one shall keep "pecking away" in the effort to wear down a serologically or symptomatically resistant case can never be given a general answer If the patient takes treatment without embarrassment and shows nothing to suggest a preparetic or paretic tendency five courses over a period of three years is the rough maximum.

W have discussed among ourselves number of times conception of periodic courses throughout life, but have always ended by opposing them on the belief based on experience, that some of the worst wrecks, physically and mentally in the general field of syphilis are the victims of the subcurative treatment habit. The question as to how far one shall try first this, then that, stepping up the intensity till nothing remains but malaria and tryparsamide for patient who at the outset showed no indications calling for either of these procedures, is problem susceptible of decision only after the fullest study of the individual case. In general, intensification in the absence of contraindications is preferable to long-drawn prolongation both from the standpoint of the patient morale and his finances—but the potential risks outweigh in decision, all told, both morale and finances.

Intraspinal Treatment Phase.—The restricted usefulness of intraspinal therapy as means of attacking localized processes, such as lower cord tabes with lightning pains, an apparently isolated meningeal lesion, or seemingly focal process such as primary optic trophy is apparent in the table. Special equipment and experience are essential in using intraspinal therapy and its present limited field does not justify its use under unfavorable working conditions as desperation measure Kierland and O'Leary (1941) revival of this procedure will be mentioned later (see p. 1049) and Viets believes that intracisternal Swift Ellis treatment may be reduced to the simplicity and status of an office procedure. If the complexion of the case is favorable, t to three or t most ten to twenty treatments should, except in primary optic trophy show definit therapeutic results. In no case have we felt disposed to use the long series of intraspinal treatments (forty or more), hich have occasionally been employed. The usual intraspinal course consist of four or five treatments at bi-weekly intervals, repeated in three to four months. In primary optic atrophy the treatment should be prolonged.

In only [illegible] per cent of our meningeal cases of neurosyphilis was any resort to intraspinal therapy necessary to secure permanent good result within the t to seven years of our observation. In only 10 per cent ere series of twenty or more such treatments given. In cerebrospinal syphilis intraspinal therapy was found necessary in [illegible] per cent and series of twenty or

these unit courses to meet individual situations. Intensification begins with the substitution of arsphenamine (606) for neoarsphenamine (914) With the advent of tryparsamide and fever therapy the method of doubling the

Fig. 763

SOME RECOGNIZED COMBINATIONS IN AMERICAN PRACTICE IN THE THERAPY OF NEUROSYPHILIS

1 Standard treatment alone (see Fig. 764) Indicated in first year to eighteen months of most infections and in rapidly advancing acute local processes with marked therapeutic shock risks (N III, N VII, meningitis, low tabes)

2. Standard treatment plus intraspinal Swift Ellis treatment in 5 injection courses for 8 to 20 treatments.
   Indicated especially in low tabes with marked ataxia, severe lightning pains, early optic atrophy

3. Standard treatment *for six months to one year followed by tryparsamide either* (*a*) in 10 injection courses with coincident mercury salicylate and four to six weeks' rest between courses; or (*b*) one to two years or more periodic combination with mercury or bismuth. *Spinal fluid examination every six months.*
   Indicated (1) As a conservative course in late latent or resistant neurosyphilis, including the "paretic formula"; (2) in the presence of malarial contraindications (3) in the presence of other active forms of syphilis; (4) in the first two *to three years of the* disease as protection against relapse, infectiousness, progression in other structures, (5) where institutional management is inaccessible.

4. Standard treatment 1 to 2 courses, malaria 12 to 15 chills, quinine and *standard treatment* 1 to 3 courses, or neoarsphenamine alone. Spinal fluid examination every six to twelve months.
   Indicated Robust young preparetics ("red flag"), and early paretics, especially *after* the fourth to sixth year of the infection, avoiding tryparsamide risks to vision. Viennese type of course.

5. Standard treatment, 1 to 2 courses, malaria 12 to 15 chills, quinine; tryparsamide either in courses or continuously one to t o years or more.
   Indicated Where well-defined symptoms of paresis have ppeared, or the patient has serious neurosyphilis, asymptomatic or symptomatic, and ill soon pass out of the optimum age period for malarial therapy

6. Tryparsamide from the start in moderate doses, 10 to 20 injections, followed by malaria, 4 to 8 chills, quinine neoarsphenamine, malaria repeated, standard treatment or tryparsamide.
   Indicated In the debilitated paretic (Poole) The broken malarial course is coddling device the initial tryparsamide for tonic effect.

7 Malaria without preparation, followed by quinine and neoarsphenamine (8 to 5 injections), then tryparsamide
   Indicated A standard institutional type of course for robust paretics.

8. Systems 4, 5 6 and 7 followed by (*a*) malarial reinoculation or (if immune) by typhoid vaccine fever cabinet.
   Indicated In clinical (not necessarily serological) failures.

9 Standard treatment combined with ( ) typhoid vaccine or hot baths.
   Indicated ( ) where equipment for other method here is lacking, or special facilities exist (diathermy) (*b*) here malaria is contraindicated, tryparsamide refused or non-cooperation makes it risky ( ) for special symptoms in neuro- and late syphilis, *e.g.* lightning pains, crises, malignant tertiarism, obstinate bone and eye lesions, serologically f st cases.

arsphenamine and heavy-metal dose (inunctions) and halving the interval in the treatment of paresis, may now be regarded as superseded.

The Decision to Intensify Treatment.—*The* decision to intensify by a shift to a treatment method involving greater risk whether to eyesight (tryparsamide) or t life (pyrexial therapy) may often be the basis for con-

syphilis, tryparsamide and intradural therapy are about equally effective and both much more so than routine treatment (3) that malaria is much

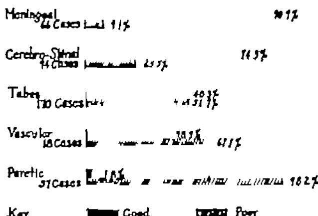


Fig. 706.—Results in treatment of neurosyphilis without tryparsamide or malarial therapy (Stokes and Shaffer)

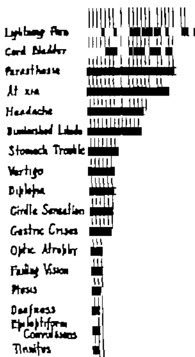


Fig. 707.—Relative frequency of common symptoms in neurosyphilis as major complaint. One space equals 5 cases.

the best treatment for paresis and taboparesis (4) that malaria and tryparsamide are more effective in tabes than routine treatment (5) and that primary optic atrophy may be arrested in numerous cases by intraspinal

therapy after all other methods have failed. Moore's further studies (1942) have led him to prefer malaria.

Response of Specific Symptoms of Neurosyphilis to Standard Treatment.—The results obtained by the Mayo Clinic service as summarized by Shaffer and Stokes, are still, in spite of the newer treatment agents, fairly representative of what may be expected in behalf of the individual patient. In Fig. 767 the relative frequency of common symptoms in neurosyphilis as chief complaint is presented, and in Fig. 768 the percentage of good clinical response. Special methods of dealing with individual refractory complaints are considered in subsequent section.

Location and Accessibility of Lesions, in Relation to Therapeutic Response.—In general it may be said that the recovery of the neurosyphilitic patient appears to depend upon the ratio of active inflammatory process to

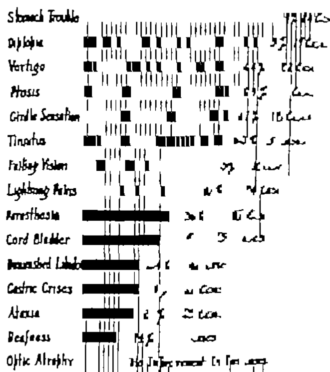


Fig. 768.—Percentage of good clinical response secured in various symptoms of late neurosyphilis. One space equals 2 per cent.

degeneration at the time treatment is begun. It is dependent, too upon the location of the lesion and its accessibility to local or circulatory approach. The approachability of the base of the brain and the meninges through their rich blood supply makes for the ready response of headache, diplopia, and ptosis and of the various paresthesias which express irritation of the spinal roots. The relatively poor prognosis of chronic anterior poliomyelitis of neurosyphilitic origin as compared with tabes dorsalis is a consequence of the direct attack of the disease upon the parenchyma of the nervous system (motor neuron) in the former and the somewhat less direct approach via the meninges, in the latter. Thus, too, a recovery of light reaction in an Argyll Robertson pupil or of absent knee-jerks in a myelitis will depend upon the location and the inflammatory character of the lesion. Both Spiller and

Stokes have seen the Argyll Robertson pupil recover and they regard this as evidence that the lesion is peripheral and not nuclear. Healing changes may as in the cardiovascular system, leave a symptom unchanged or accentuated, or as in the development of cortical epilepsy following the healing of pachymeningitis, substitute a new one for it. Many of the conflicting statements made regarding the outlook of optic atrophies, due to failure to distinguish the primary degenerative lesion of tabes from the secondary degeneration following optic neuritis in other forms of neurosyphilis, require critical revision. The outlook of secondary atrophy is proportional to the degree of neuritis still present when treatment is begun, and is often surprisingly good. The outlook of the primary degenerative type is, of course far more grave.

Serological Responses in Neurosyphilis Under Treatment.—In dealing with the more benign forms of neurosyphilis reduction of the spinal fluid and blood abnormalities to normal, side by side with symptomatic improvement, is common observation. It is also well known that clinical relapse is forewarned or accompanied by serological relapse. This marked parallelism in serological results cannot, however in the present state of knowledge, be carried over full force into the interpretation of serological as compared with clinical improvement in general paralysis. Practically all observers are agreed that while striking remission and even clinical cure as determined by economic rehabilitation criteria, may take place in the first year of general paralysis under treatment, the reduction of serological tests to normal requires from two to five years with an average of approximately four years from the institution of treatment, granted that it occurs at all.

The current statistics such as those of the CCG (Kierland, O'Leary and Vandoren 1942) must be quoted in their entirety to show the trends and even then seem to contain sources of statistical error such as nonexamination after fluid once becomes normal, no data of deaths and lapses, which permit only the general statement that the spinal fluids of tabes and taboparesis are the most resistant, those of meningeal and meningovascular syphilis the least resistant. Tabes occupies middle ground, the percentage of reversals ranging from 33.8 to 60 per cent in gradually ascending see-saw scale. It was clear in this study as in others, that serologic improvement or complete reversal does not necessarily go hand in hand with good clinical results. In the published material, the shortness of the period of observation in the larger groups of cases greatly weakens the ultimate conclusions.

The Fever Committee of the Cooperative Clinical Group (J.A.M.A. 115 677 1940) reported the following:

SEROLOGIC RESULTS

1 Reversal rates for originally positive spinal fluid and blood increased as the duration of treatment-observation increased.

2. Positive blood reversed more rapidly though not in greater proportion than positive spinal fluid. The degree of spinal fluid abnormality on beginning fever therapy influenced the proportion of expected reversals.

3. In patients treated with fever plus chemotherapy the annual rates of spinal fluid as well as blood reversal were consistently higher with malaria than with artificial fever but this difference was assumed to be due to the greater amount of chemotherapy (17 per cent more) administered to the malaria patients. Without the use of auxiliary chemotherapy there were no differences between the spinal fluid and blood reversal rates of patients treated with malaria and those treated with artificial fever

4 Blood as well as spinal fluid reversal rates were at least twice as great with as without the use of auxiliary chemotherapy Among patients not treated with auxiliary chemotherapy 46 per cent of all spinal fluid reversals subsequently relapsed as contrasted with only 24 per cent spinal fluid relapses among patients treated with auxiliary chemotherapy

5. Two thirds of all the relapses from spinal fluid reversal occurred within one year following the original reversal.

6. Negative blood serologic reaction did not indicate the status of the spinal fluid, but persistently positive blood serologic reaction was indicative of positive spinal fluid reaction.

RELATION OF CLINICAL TO SEROLOGIC RESULTS

1. Reversals of both blood and spinal fluid were associated more than twice as frequently with clinical success as with clinical failure. However, since clinical success was not accompanied by complete reversal (blood and spinal fluid) in 42 per cent of the cases it follows that clinical success was not necessarily dependent on serological reversal.

2. Reversal of the spinal fluid was more important than reversal of the blood in indicating the chances of complete clinical recovery.

3. In three fourths of the cases with clinical as well as serologic recoveries, the clinical remission preceded or occurred during the same year as the serologic reversal. When the clinical remission preceded the serologic reversal, it did so by an average difference of from two to three years. In the remaining fourth of the cases in which serologic recovery occurred first, an average of from two to three years elapsed before clinical remission was obtained.

Even, however, while we concede the lack of harmony between serological and clinical results in this special field of neurosyphilis, there is still reason to look forward to and to seek serological improvement in the paretic under malarial or tryparsamide therapy by analogy with the parallelism of clinical and serological results in benign forms of neurosyphilis. Such response should be looked for and an examination of the spinal fluid not less frequently than once in twelve months, and preferably once in six months, is a necessary part of the control of treatment in all forms of neurosyphilis.

In the majority of cases showing improvement, the spinal fluid cell count, the hyperalbuminosis, the colloidal tests, tend to subside toward normal with treatment, and the spinal fluid Wassermann becomes weaker, positive only in larger and larger amounts of fluid until it becomes negative in the generally accepted quantitative procedure. A persistently positive Wassermann reaction in the spinal fluid, as in the blood, suggests a resistant case, and should not be lightly dismissed as of little moment, though it may be perfectly proper, after a reasonable amount of treatment, to allow a more or less prolonged rest interval to decide whether the finding is significant or not. In all Wassermann testing of the spinal fluid for therapeutic purposes a quantitative procedure measuring grades of positiveness is of great help. We have seen repeatedly relapse occurring in patients whose tests were negative on smaller concentrations such as 0.3 or 0.4 cc. and who later remained normal for long periods when the test became negative on 1 cc. with a cholesterinized antigen. The fact that the lumbar fluid is not always an index of the condition of the entire nervous system must be borne in mind, of course.

Behavior of Cell Count.—Cell count under treatment tends to increase with unfavorable progress or rises in an unknown proportion of cases as a temporary flare-up of the Herxheimer reaction. It is unusual indeed to see in early cases persistently normal cell counts and persistent strongly positive findings in the other three tests. On the other hand, in late cases this combination is not uncommon. A few patients with long-standing processes never seem entirely to regain a normal count, and hover about 4 to 8 cells without, however, being any the worse for it within the period of our observation. The more pronounced abnormalities have, however, seemed to us important for observation at least. We have watched slight and even moderate degrees of spinal fluid abnormality, heralded by slight rises in cell count, sometimes even with a paretic trend, resist the utmost resources of treatment and persist over a period as long as ten years without advance of symptoms.

On the other hand we have seen to our regret, cases in which with Grade III spinal fluids at the outset, we have allowed a quick reduction to a mild grade of abnormality to lead us into withholding the utmost resources of treatment (fever) The result was a slow degeneration and symptomatic progression under a mask of serologic benignity maintained by repeated but always inadequate treatment.

Blalock and Hinsie (1936) found that the earliest serologic changes in paretic spinal fluids occur in the cell count, and Maletz and Solomon (1937) found the cell count normal at the end of one year in 80 per cent of their cases of paresis treated with malaria and tryparsamide. They noted that once the count was normal it rarely became abnormal again. A sharp rise in cell count on reexamination is referred to as meningeal relapse, and its repetition time after time is to us an earmark of resistant neurosyphilis. Stokes and Shaffer found that 9 per cent of their early meningeal, 5 per cent of cerebrospinal, and 20 per cent of their paretic cases, showed such relapses. While the symptomatic significance of the cell count is sometimes denied, we have had too many patients of reasonable intelligence able to predict, from the revival of their symptoms, almost the exact count of their fluids, not to accept this warning as sign of relapse. It is not, however, invariably accompanied by symptoms, and again may precede by months or years the ultimate appearance of definite paretic changes. The irreducible or see-saw cell count (Fig. 780) is, in our experience, an unfavorable sign.

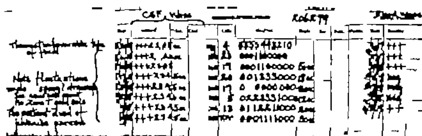


Fig. 780 —The least responsive type of spinal fluid, Wassermann strongly positive to 0.2 cc., low cell count (before treatment) and first zone gold sol.

The question as to whether the cell count is invalidated by local reaction following repeated lumbar puncture can in general be answered for our experience in the negative, provided not more than 10 cc. be removed each time and the interval be not less than week.

Colloidal Tests.—The colloidal tests must not be too closely read during treatment or minor variations given unjustified significance While colloidal reactions tend to subside toward normality as the patient improves, and a first zone test may change to a second zone and finally become negative entirely the margin of technical error is large enough especially in the gold sol, to require repetition to confirm any particular finding A reported reading below 5 from our laboratory in the first tube of the colloidal mastic test (as 3555543100) has repeatedly accompanied taboparesis with primary optic atrophy A first zone curve may gradually develop in a series which was at the outset of second zone type, and intervals of second zone tests may separate first zone tests which in view of the outcome of the case, more truly expressed a tendency toward paresis.

The colloidal test according to many observers since 1919 (summarized by Maletz and Solomon, 1937), and Moore (Text 1943) is the last of the tests to become negative (preceded by cell count, protein and Wassermann in order named). W concur in the general order but believe the Wassermann equally resistant, and the slightly elevated cell count sometimes likewise, in some individual cases.

Stokes and Baughn reached the conclusion that even though blood serum had been introduced into the canal by intraspinal treatment two weeks before, a strongly paretic fluid still retained its characteristics, and a nonparetic fluid was not in general made to yield a paretic gold sol unjustifiably. The colloidal benzoin and mastic tests, while less delicate, seem to be more constant in their expression of cerebral involvement than the gold sol.

Fig. 770.

PROGNOSIS OF HIGH AND LOW CELL COUNTS WITH FIRST AND SECOND ZONE GOLD SOL CURVES. (Stokes and Baughn.)

	Cell count.	Cases.	Improved, per cent.	Not improved, per cent.
Zone I.	High	51	38	62*
	Low	16	19	81
Zone II	High	49	65	35
	Low	19	63	37

No data in 3 cases.

Unfavorable Combinations.—The combination of cell count and colloidal test was studied by Stokes and Baughn as a result of the impression that low cell counts and first zone gold sol reactions tended to indicate an unfavorable prognosis. While their series was small, such a tendency seemed definitely apparent, and is expressed in Fig. 770.

Fig. 771.—Response of an abnormal spinal fluid to treatment, with ultimate return to serological normality. The rise in cell count following spinal puncture is a curiosity in our experience. The patient was a child with juvenile tabes who made a complete recovery. Under observation five years. Twelve intraspinal treatments.

From this figure it is apparent that the patient who has a low cell count with a first zone colloidal test and the usual accompanying strongly positive blood and spinal Wassermann reaction, has the poorest outlook therapeutically while patients with second zone colloidal tests have a very much better prognosis.

Globulin Test.—The importance of increased globulin must be largely redetermined in the light of more exact total protein estimations. Ayer

Solomon, and others have suggested their value as an index of return to normal.

Maletz and Solomon (1937) noted that gradual reduction in the amount of total protein in the spinal fluid occurs under malarial and tryparsamide treatment so that at the end of one year the total protein reached normal level in one third of their cases. But after five or even ten years, 40 per cent of the cases showed elevated total protein. They noted that to some extent the height of the total protein was an index of the final figures and concluded that the higher the initial level, the smaller is the likelihood that it will become normal. Blalock and Illness (1936) *felt also that the decrease to normal of the protein occurred less frequently than the cell count.*

Blood Serological Tests.—In the more benign forms of neurosyphilis, the blood serological tests should be comparatively easy to reverse if positive Even in the more severe forms reversal may occur in the majority of cases in about five years after treatment is instituted Their predisposition toward the negative in vascular neurosyphilis should be recalled. A persistent positive serological reaction in neurosyphilis suggests either paresis, a cardiovascular or a visceral lesion The use of the Kahn and Kline precipitation

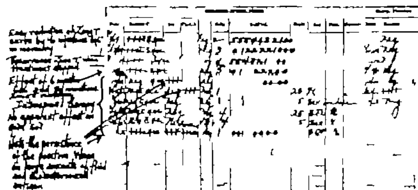


Fig 772.—An illustration of the importance of the quantitative Wassermann test on the spinal fluid, and of the ease with which first zone gold sol test may sometimes be "reduced" to negative by treatment.

procedures and their presumptive or sensitized modifications in the evaluation of the treatment of neurosyphilis is not as yet worked out.

Value of Repetition of Tests.—Spinal fluid findings gain meaning from repetition, and, in fact, can rarely be safely judged from single tests. It is the long series of tests in a single case, covering a period of years, which is really informative and yet which must never be disproportionately valued

Special Treatment Methods in Neurosyphilis

Indications, Contraindications, Technic, Results.—In beginning this discussion of the most recent advances in neurosyphilotherapy let it again be recalled that there are no exclusive methods in the field. Each and every method has its zone of particular effectiveness and two or more methods are more usually appropriate in an individual case than exclusive adherence to one alone

The rationale of the various methods here discussed has been taken up to some extent in connection with the general principles of the treatment of

syphilis and in the discussion of the various drugs and technical procedures, including nonspecific therapy

Spinal Drainage, Intraspinal and Cistern Therapy.—We believe that the controversy over the relative merits of spinal drainage and intraspinal therapy may be said to have resolved itself into approximately the following residue: Spinal drainage may be employed in treating neurosyphilis by standard methods but has very restricted field of usefulness and should not be employed as a substitute for the newer methods in refractory cases or in those showing a preparetic or paretic tendency In the main it is less effective than Swift Ellis intraspinal ther

Fig 772.

THE TABETIC PATIENT AS A POTENTIAL UREMIC

Male, aged fifty-tw years.

Diagnosis of Tabes Dorsalis in 1911
Complaint: Frequent micturition.
Cystoscopy shows atonic bladder Violent febrile reaction.
Blood Wassermann Positive. Given inunctions.
Three arsphenamin injections 1912.
Re-examined 1913. Bladder and urine not considered.
Two arsphenamin injections 1914.
Re-examined 1915. no special complaint of bladder or urine, not examined.
Re-examined 1916. Says bladder better Syphilologist verlooks blood and pus in urine

Re-examined 1917 Blood Wassermann positive After 5 injections arsphenamin, bladder and lightning pains much improved.
Blood and Pus in Urine Still Ignored.
Re-examined 1918. Spinal Fluid Negative
Re-examined 1919. Trace of blood and pus in urine.
Patient at last sent to urologist.
Urine: Albumin, moderate amount. Microscopic blood (trace). Much pus.
Phenolphthalein Excretion 10 per cent.
Blood Urea: 61 mg per 100 c.c.
Residual Urine 32 ounces.

Patient refused to see urologist and returned home.

Six weeks later physician wired that he was seriously ill with vomiting and hiccup, urin very cloudy much albumin. Patient died in coma.

DISCUSSION

The diagnosis is obviously in retrospect, terminal uremia. Note that the arrest of this patient tabes was complete.

Urinary retention due to atonic ("cord") bladder is exactly as serious *factor* **in the** life expectancy of the tabetic patient as in the patient with prostatic hypertrophy It should be similarly managed.

Th **functional tests should be done early in every tabetic, and infected bladders and** retention properly treated by instruction and, if necessary catheterization and irrigation.

Catheterized *functional* **tests only are** *reliable in these cases.*

The *life* **of an arrested tabetic may** *depend* **on his bladder.**

apy as, for example, in the material studied by Osborne nd Stokes. In carrying out spinal drainage quantities of fluid ranging from 20 to 60 cc. over and above the amounts required for ordinary test purposes may be withdrawn. The patient should lie on his side and no attempt should be made t aspirate fluid. Drainages may be repeated weekly or once in two weeks, though intervals as long as six eeks have been employed, probably without material effect. Complications are rare even headaches not being any more frequent, if as frequent as after ordinary lumbar puncture Reports of precipitation of generalized neurosyphilitic manifestations are rare (Jahnel, Handbuch) Of the various intraspinal procedures available including the introduction of arsenic in the form of arsphenamine, neoarsphenamine, arsphenaminized serum reinforced with arsphenamine (Ogilvie modification) and tryparsamide, we believe that opinion has pretty well simmered down t the use of the Swift Ellis auto-arsphenaminized serum to the exclusion of the

This case, despite its ancient date-line, is retained as one of the eternal verities.

Fig. 774.

CEREBRAL GLIOMA WITH FATAL TERMINATION IN A PATIENT WITH SYPHILIS. EPILEPTIFORM ONSET CONFUSION WITH NEUROSYPHILIS. TRANSIENT IMPROVEMENT UNDER ANTISYPHILITIC TREATMENT

Male, aged thirty-five, clergyman.

Date Examined May 9, 1919
Chief Complaint Swollen knee.
History: The early history of this case is given in Chapter XV to illustrat the impor tance of taking blood Wassermann tests in synovitis before operative interference The patient remained under treatment for four years and during that time his case underwent the following developments
Synovitis of the Knee: Given 9 arsphenamin injections and 40 inunctions. Disappeared from observation.
Returns eighteen months later complaining of dizziness and convulsions.
Neurologic examination two years before had been negative, with negative spinal fluid.
Pupils now slightly retarded and unequal. K. J. slightly increased, hypogastric decreased -ray of head negative; no aura.
Indeterminate diagnosis Grand mal (?)
Returned fifteen months later Series of arsphenamin injections elsewhere less than one month go. Convulsions disappeared, but now has severe bilateral frontal headaches and failing memory; involuntary bowel movements occasionally; will not talk; walks slowly; slight staggering; voice normal; 20 pounds weight loss; has never been right mentally since last arsphenamin injection given when he had fever of 101 F Patient drowsy all the time. Spinal fluid negative.
Neurologic Examination Left eye deviates on convergence. Pupils slower than on previous examination. Bladder control much reduced. Biceps and patellar reflexes increased Cremaster and bulbocavernous reflexes decreased. Marked tremor; slurred speech and difficulty with speech tests. Slight sensory disturbances in perineal region.
Neurologic diagnosis before spinal fluid examination was "dementia paralytica or severe meningo-vascular syphilis. After negative spinal fluid examination diagnosis of paresis unlikely May have neurosyphilis, but cannot be certain. Incontinence hard to interpret, as objective findings are almost all over sacral distribution.
Later neurologic opinion under hospital bservation "Essentially an encephalitis, but whether syphilitic or otherwise we cannot say May have softening of the silent area due to thrombosis in addition to old findings. Nothing especially characteristic of epidemic encephalitis. Would have to place question mark after any C. N. S. diagnosis made. Would treat him for lues if any other findings indicate.
Placed on treatment for syphilis, given 40 injections mercury succinimid grain ⅙; 30 injections sodium iodid, 10 grams daily 5 injections arsphenamin 2 to 4 decigrams.
Result, marked improvement Became well oriented, remembers present and past events, but his speech is slow and tremor of lips persists. Headache disappeared.
Neurologic comment, "Would continue to treat as for lues. This patient may have brain tumor but lues seems undoubted. Get fundus examination. Examination fundus—hyperemia and edema of disks (1 diopter right, 2 diopters left); apparently choked disk.
Neurologic examination five days later—frontal lobe syndrome. Gradual deterioration, death two weeks later.
Postmortem examination—glioma of frontal lobes of cerebrum with gliosis Syphilitic aortitis with advanced arteriosclerosis cardiac hypertrophy ith moderate dilatation.

Discussion

The neurologic comments show in the clearest possible way the difficulty in distinguishing objectively between syphilis and frontal lobe tumor.

Note especially the repeated improvement in the patient neurologic symptoms under treatment for syphilis.

The negative spinal fluid is compatible with vascular syphilis of the brain and has been repeatedly seen in patients who at autopsy show incontestable evidence of vascular cerebral syphilis.

The negative spinal fluid practically eliminates general paresis.

Note that in all the numerous physical examinations to which this patient was subjected in the period of four years, not once was his cardiovascular condition (advanced aortitis and arteriosclerosis) ever suspected.

His blood-pressure was repeatedly found to be within normal limits, 120/80, and no murmur was ever recognized.

Non-specific effects of treatment for syphilis must be guarded against in the therapeutic test with arsphenamin, mercury or iodid in an effort to differentiate cerebral vascular syphilis from encephalitis and frontal lobe tumor

other enumerated methods. There seems no reason for introducing nonspirillicidal drugs such as tryparsamide into the spinal canal, and much of the action of mercurials, for example, must be that of exciting aseptic meningitis (cf Kierland and O'Leary 1941).

In administering intraspinal therapy in present practice, the indications include (1) moderate resistiveness, especially of the meningeal phase of early meningovascular neurosyphilis (2) low tabes with bladder and sexual disturbances and marked lightning pains and ataxia (3) basilar meningitic lesions, including isolated cranial nerve involvement in which the technic should be that of Gennerich the patient being kept with the buttocks high and head low for some time after the performance of the intraspinal injection (4) primary optic atrophy (Moore contra, 1942)

Among the contraindications should be included (1) especially rapidly advancing bladder sphincter difficulties (2) acute cerebral processes with increased intracranial pressure (choked disk) (3) rapidly progressive ataxia and advanced tabes dorsalis (4) patients in whom reactions from the treatment are more severe than those resulting from ordinary lumbar puncture (Kierland and O Leary 1941 with which our experience is not entirely in accord since we have almost no reactions to puncture and some leg pains after Swift Ellis) Gastric crises in general are not particularly responsive to intraspinal therapy and severe attacks may be precipitated by the procedure. Inexperience with the method is always a contraindication to its use for it is distinctly the province of experts.

Intracisternal and intraventricular therapy was extensively employed in the treatment of paresis and primary optic atrophy but has been largely superseded both because of its technical difficulties and its risk. If employed, the Swift Ellis procedure is the only one we consider even reasonably safe and we believe equally good results can be obtained by the Trendelenburg posture in intraspinal therapy or by the Gennerich double-puncture technic (page 328) Moore speaks of the intracisternal route as probably" valuable in primary optic atrophy

Tryparsamide Therapy of Neurosyphilis

Therapeutic Use of Tryparsamide in Man.—Tryparsamide in syphilology at the present day is a one-purpose drug. Its field of effectiveness is limited to neurosyphilis and conspicuously to early and active paresis. Moore, Robinson, Keidel, and Lyman (1924) showed conclusively that the drug is entirely ineffective in all other aspects of systemic syphilis except that of the nervous system and that its use even in early neurosyphilis associated with secondary cutaneous and mucosal lesions without reinforcement by other forms of treatment may be associated with recurrence continuance of active lesions and even some forms of relapse There is no evidence that the drug has any preventive effect in the control of late neurosyphilis, but this question has not had systematic investigation

The drug has, incidentally marked tonic properties and eight gains are to be expected. Not infrequently it is necessary for the patient to be completely retailored, if in poor condition at the outset. There are also definitely stimulative effects pon the sexual centers observable in even comparatively normal individuals, but this should not be taken as endorsing it to the public as an aphrodisiac

Methods of Administration and Dosage.—Tryparsamide is administered intravenously the therapeutic dose being dissolved in 5 to 10 cc. of water

prepared under all the precautions appropriate to arsphenamine. Jamot describes its subcutaneous use in trypanosomiasis with occasional abscess formation only. The method, however, is not advocated. The crystalline drug can be dissolved in ampule by a technic similar to that for any of the more easily soluble arsphenamines, the large ampule favoring this use. The dosage of the drug comes as a distinct shock to one accustomed to an arsphenamine scale, ranging as it does from 1.0 Gm. to 5.0 or even, on rare occasions, to 7.0 Gm. with an optimum adult dose of 3.0 Gm. (0.04 Gm. per kilogram of body weight). Lorenz and Reese, whose experience is enormous, particularly caution against the use of doses less than 1 Gm., stating that they are definitely irritative and hasten the progress of the disease. The total amount of the drug given in successful cases ranges from 48 to 1500 Gm. (Lorenz).

Prolonged Treatment.—Tryparsamide makes no impression, or an actually unfavorable one when given as a scattering of injections or a single short course. The best clinical and serological results all observers agree, do not appear until after 70 to 100 injections. It is a matter not as yet definitely settled whether these should be given in broken courses or continuously, but either technic may be accepted as satisfactory according to the circumstances and individual indications. Cady and Alvis believe that high dosages and long series tend to favor eye complications, but while too large preliminary dosage may be important, there is much evidence that eye complications are most frequent during the first ten injections and that thereafter a series may be indefinitely continued with little risk of trouble from this particular complication. Vigilance should not, however, be completely relaxed after the tenth injection since a patient on our service had tryparsamide visual disturbances on the eighty-second injection (Beerman and Shaffer, 1940). Others have noted similar cases. Downs and his associates (1941) found that 31 per cent of the objective visual disturbances among their 223 patients occurred late in the course of treatment, one case after 113 injections. Reese (1940) insists, however, that tryparsamide must be used week after week for a period of years. Tryparsamide treatment is not an exclusive form of therapy. It may be used to advantage in alternation with courses of standard treatment if indicated by the general status of the syphilitic infection, or in alternation with fever therapy or as a sequel to it if indicated by the status of the neurosyphilis. The original Lorenz Loevenhart technic prescribed the use of mercury salicylate in 1-grain doses weekly, and many observers still continue this synchronous use of the mercurial. Bismuth may likewise be thus employed, either between the individual tryparsamide injections or simultaneously with them.

Complications in Man.—Tryparsamide, aside from its optic nerve damage, was considered to be so reactionless that Lichtenstein rated its innocuousness ironically as a positive drawback to the popularization of the drug. Recently there has, however, been an apparent increase in the observed frequency and severity of various reactions (Moore, 1939; Traenkle and Dalce, 1939; Hinrichsen, 1939; Beerman and Shaffer, 1940; Kopp and Solomon, 1940; Downs, McDermott and Webster, 1941). There has perhaps been a tendency to overemphasize the minor ones.

The reactions produced by the drug are summarized in Fig. 775.

Downs and coworkers found that 80 per cent of the nitritoid reactions (their most frequent reaction) occurred late in the course of treatment and repeated reactions necessitated stopping therapy in 42.2 per cent of their

223 cases Kopp and Solomon (1943) found that the use of tryparsamide immediately following fever does not increase the amount of liver damage or delay repair The Cooperative Clinical Group in an experience of 19,964 injections noted 0 35 cases of jaundice per 1000 injections.* The incidence of crustaceous dermatitis from tryparsamide is according to the Cooperative Clinical Group, 0 15 per 1000 injections. Epstein (1941) found in a comparison of the various arsenical antisyphilitic drugs that in regard to total skin reactions mapharsen was apparently second only to tryparsamide in relative freedom from paratherapeutic cutaneous complications. While it is generally safe to use tryparsamide when indicated in a patient who has recovered from trivalent arsenical dermatitis, the possibility of polyvalent sensitivity previously mentioned should be recalled.

Our material (Beerman and Shaffer 115 cases) contained 10 patients who sustained one or more systemic reactions to tryparsamide. There were no

Fig 775.

COMPLICATIONS OF TRYPARSAMIDE THERAPY

1 Local slight burning, no necrosis.
2 Abscess: subcutaneous use 1.6 per hundred cases. Method not recommended.
3. Dermatitis occasional, mild. The drug may occasionally be used after trivalent arsenical dermatitis.
4 Fixed exanthem (rare) Urticaria (rare) Herpes Zoster (occasionally)
5 Nausea, vomiting, diarrhea, cramps.
6. J undice and hepatitis mild incidence 1 to 10 per cent of cases. (3.8 per cent Kopp and Solomon.)
7 Nitritoid crisis, dizziness, sickness. (Nitritoid reaction may occur after much tryparsamide therapy Kopp and Solomon.)
8. Possible slight irritation of abnormal kidneys.
9 Neuritis (rare)
10. Idiosyncratic intolerance: loss of weight, increased irritability confusion, coma.
11 Therapeutic flare-up (Herxheimer) del yed to fourth t eighth eek may require incarceration of disturbed patients.
12. Eye complications: toxic trophy or amblyopia.

TRYPARSAMIDE TREATMENT IS TONIC;
USUALLY UNEVENTFUL AND UNSPECTACULAR

local reactions. The reactions we observed included loss of weight (2 cases) severe nitritoid crisis (4 cases) nausea and vomiting (7 cases) itching or patchy dermatitis (4 cases) headaches (1 case) jaundice (1 case) nervousness (1 case) neuralgic pains (1 case)

Occasional patients show what might be regarded as idiosyncratic reactions to tryparsamide. That is, without apparent reason they tolerate the drug poorly lose weight become nervous and restless and confused a prompt improvement ensuing when the drug is stopped In such cases it is best to discontinue its use entirely

Therapeutic Shock Effects from Tryparsamide.—An earlier suspicion has grown into certainty on this point. There can be no reasonable question that the drug produces symptomatic exacerbation in neurosyphilis which is especially disturbing and vexatious in the first six to ten weeks of the treatment of the disturbed patient This evidence that therapeutic flare-up occurs

Gastrointestinal reactions ere encountered in 7 1 per cent of Kopp and Solomon s patients.

has led to reduction in the initial dose and to increasing it gradually We believe with Cady and Alvis also that this measure, together with intensive preliminary preparatory treatment by the use of mercury bismuth, and the

Fig 778.

THE EYE COMPLICATIONS OF TRYPARSAMIDE

1. Comparatively frequent at the outset, they are still too common t the hands of the inexperienced and careless physician who does not apply ophthalmologic control.
2. The injury is presumed to be as with atoxyl, to the third neurone of the optic tract. The effect is an optic atrophy with visual loss first, disk changes later
3. Complications more frequent in abnormal than normal eyes (Cady and Alvis, 1.5 per cent vs. 37 per cent Hinrichsen, 2.9 vs. 22.7 per cent).
4. Primary optic atrophy however is not an absolute, though relative contraindication (Woods and Moore, Cady and Alvis)
5. Choroiditis is not a contraindication (Stokes and Wilhelm, Hadden and Wilson). (Especially if vitamins used, Muncy)
6. Two types of symptoms subjective, followed by objective.
7 Two types of outcome transient with recovery; permanent impairment, partial or complete. The former is much the more common. Vision may ultimately even improve over outset.
8. Subjective symptoms include dimming of vision, grayness, ground glass effect, dazzling (as of sunlight on snow), an appearance as of clouds or "waves approaching from the periphery of the visual field, and uncertainties in gait suggesting poor vision.
9 Objective symptoms include: mild cases with reduced visual acuity concentric or sector contraction of visual fields, unilateral or bilateral, partial or complet recovery; severe cases, total amblyopia with ultimate complet optic atrophy
10. Risk of eye complications decreases rapidly after the first course nd is negligible, *though not completely nil* after the tenth injection.
11. Suspension of treatment for month following subjective symptoms may make continuance of the drug possible (Cady and Alvis) but is not without risk.
12. Preventive measures:
    - (a) Insist on the proper ophthalmological control and complet eye examination before visual acuity tests and perimetric fields (not rough tests) *during* the first series of 10 injections. Check before each injection (fundus examination alone not trustworthy).
    - (b) Enlist patient cooperation if condition permits and protect yourself by explaining risks and symptoms and obtaining consent (some therapists disapprove).
    - (c) If cooperation of patient not obtainable, risk is much increased.
    - (d) Begin with moderate doses (1 Gm.) and have preparatory treatment with "606" and bismuth if possible.
    - (e) Question the patient each time before injection.
    - (f) Have the ophthalmological report at hand before each injection up t the sixth or tenth. Unnecessary except occasionally thereafter.
    - (g) Stop treatment immediately if subjective symptoms appear Do not wait for objective changes.
    - (h) Do not treat pregnant women with tryparsamide W have no knowledge of the effect on the child' eyes.
    - (i) Caston has suggested "forced" spinal drainage as treatment.
    - (j) Vitamins especially the B complex (Muncy) and B_1 (Boley and Albers). (Experimentally suggested by work of McDermott et al.)

arsenicals tends to reduce both the risk of therapeutic shock and eye complications.

Tryparsamide and the Optic Tract.—This group of complications has been extensively studied, beginning with the observations of Woods and Moore, Lillie, Young and Loevenhart and subsequently of Cady and Alvis. The principal facts thus far known regarding the eye complications are sum

marized in Fig 776 The average incidence based upon a compilation of the result in the literature to date involving approximately 7500 cases is about 9.8 per cent, and the frequency diminishes with the size of the series and the experience of the therapist.

Much has been written recently on the safety as well as risks of using tryparsamide in patients with impaired eyes. Regardless of the suggestions pro or con Hinrichsen, in her invaluable review has demonstrated from the reports published from 1928 to 1938 that tryparsamide causes about eight times as many permanent ocular complications in patients with damaged eyes before treatment as it does in those with normal eyes before treatment. She found that the average amount of permanent injury to the optic nerve in cases where there was no involvement prior to tryparsamide treatment amounted to 2 9 per cent, whereas in cases with optic atrophy which were treated with this drug there was an average incidence of 22.7 per cent of permanent optic damage

The irreducible minimum of eye complications with present experience seems to range about 1 to 2 per cent. Great emphasis should be laid in prevention on the use of subjective symptoms as guides to the cessation of treatment. If for any reason the patient is unable to cooperate, either in giving account of these symptoms at each injection or in carrying through the visual acuity and perimetric field tests, the risk from tryparsamide therapy is notably increased We have never been able to reach the point, in an estimation of the innocuousness of the drug at which we are willing to give up the practice of fully explaining the situation to patients or relatives and securing from them at least a verbal assent implied by their acceptance of a letter stating the facts. Some careful observers, however have thought that this procedure increased the subjectivity of the patient and have given it up. Our most serious early mistakes arose from reliance on the fundus *examination as distinguished from visual and perimetric tests and from* failure closely to question and observe the patient

The Abuse of Tryparsamide.—The usefulness of tryparsamide is being curtailed by the unnecessary and indeed shockingly negligent occurrence of tubular vision and amblyopia in patients whose treatment was begun or carried on without ocular checks, or persisted in after their complaints clearly indicated the need to stop The drug is also misused in the treatment of early syphilis with some unsupported notion of the prevention of paresis in mind (no spinal fluid abnormalities) and in the treatment of aspects of syphilis in which no benefit can be expected (primary and secondaries)

The medicolegal responsibility of the physician in cases of amblyopia due to tryparsamide has been affirmed by a decision of the Supreme Court of Appeals of Virginia (J.A.M.A. 1941) in which it was ruled that tryparsamide is a potent drug which should be administered only under ocular control.

The Indications and Contraindications for Tryparsamide Therapy—In Fig 7— are summarized in parallel columns the indications and contraindications for the use of tryparsamide in neurosyphilis. The atmosphere of controversy which inevitably surrounds various methods of treatment within the first few years of their introduction produces an effect of pitting tryparsamide against pyrexial therapy and especially malarial inoculation. Such comparisons have their good and bad points, the latter particularly evident when prejudice leads to the use of one method to the exclusion of another where both would be applicable Even though both tryparsamide and fever therapy

are planned for a given case, the sequence inevitably involves elements of decision as to money time and energy to say nothing of appropriateness to social and other conditions. Figure 777 (tryparsamide therapy) may therefore be compared with Fig 153 (malarial therapy) for indications and con traindications.

Fig. 777

TRYPARSAMIDE THERAPY

Indications	Contraindications
1 When prolonged ambulatory treatment of noniscapacitating character in resistant neurosyphilis is possible or essential. A practitioner' method.	1 When disease of the optic nerve is present (not the vascular mechanism)
2. When expertly managed malarial therapy is inaccessible because of location, local or economic conditions.	2. When eye warning symptoms follow properly (ophthalmologically) controlled trial (1 to 10 injections)
3. Asymptomatic nonparetic neurosyphilis, when serologically resistant to 2 or 3 courses of standard treatment.	3. In paresis and preparesis when every condition favors malarial therapy
4 Paresis and preparesis, early enough to allow trial of both methods (tryparsamide and fever) if either fails.	4 When the patient responds poorly or is reactive to it.
5 Where the patient prefers eye risk to mortality risk.	5. When serological or clinical improvement is delayed more than one year and the patient is eligible for malaria.
6. I certain of the contraindications to malarial and fever therapy; especially old age, marked cardiovascular disease, active tuberculosis, diabetes, obesity severe debility (a) As preparation for malaria in debilitated patients.	6. When the patient is near the age limit or is threatened ith complications that might by delay lose him his choice of malaria as resort if tryparsamide fails.
7 As an adjunct and sequel to successful malarial or other fever therapy	7 When the patient or his family rejects eye risks.
8. Where malaria has failed to "take or the results were unsatisfactory	8. Pregnancy (effect on NII in the fetus)
9 A "last ditch resort in gastric crises.	9 Presence in patient of other active forms of syphilis (to tryparsamide alone).
	10. Marked arsenical intolerance or hepatic insufficiency?

Discussion

1 **Advantages of tryparsamide** Permits ambulatory inconspicuous, nonstigmatizing treatment, equal or only slightly inferior to fever therapy without interfering with occupation (unless patient is of irritable or disturbed type); few serious complications of NII, almost no reactions; practically no mortality as such marked toxic effect; vailable through home physician; usable where malaria may be contraindicated.

2. **Disadvantages of tryparsamide** A definite risk to vision varying with experience of physician, selection of case and control, totaling between 1 and 9 per cent (most visual disturbance temporary blindness rare) slow action, prolonged treatment necessary; therapeutic flare-up may force institutional care after all, delay if drug not effective may cost patient the chance for or full benefit of malaria.

Treatment of Tryparsamide Complications.—The management of tryparsamide complications follows the general principles described for the trivalent arsenicals. Stopping the drug in time necessitates an inquiry at each treat ment session, as to the effect of the previous injection. Since complications other than the idiosyncratic and the ocular tend to occur late after many

treatments have been given, it is usually best to give the drug up entirely rather than to take needless risks. Two months rest and a resumption at a lower dosage scale is sometimes effective While we have the impression that more patients who have had prolonged tryparsamide therapy have enlarged livers than in similar groups under ordinary treatment, Kopp and Solomon whose experience is very large, have apparently discounted this risk on the basis of functional tests.

Ocular complications are at present dealt with (1) by *stopping treatment in time* and keeping it stopped (2) by repeated forced spinal drainage (Kubie, Casten) with the administration by mouth, subcutaneously and intravenously of large amounts of hypotonic fluid (0 45 per cent Na Cl (3) the intravenous administration of thiamine chloride 50 to 100 mg at first

Fig. 778.

RESULTS OF TRYPARSAMIDE THERAPY IN NEUROSYPHILIS

Type of Neurosyphilis	Clinical Remissions: Range of Percentage	Clinical Remissions: Average Percentage
Early General Paresis	12 to 70	49 7
Advanced General Paresis	0 0 to 30	[illegible]
Taboparesis	0 0 to 80	[illegible]
Tabes	Few remissions (20 to 75 improvement)	(43 8 improvement)
Meningovascular Neurosyphilis		44 0

[1] Lorenz series restudied by Reese, 1933 includes paresis, taboparesis, asymptomatic paresis, meningovascular syphilis and a small proportion of tabes. The 135 cases which had recovered had been under observation for at least five years and represent 87 per cent of a group of 155 cases which had shown an initial favorable response to tryparsamide therapy five years previously As will be seen from Fig. 778, the drug is notably useful in tabes and taboparesis as well as meningovascular syphilis, but without any comparison with standard intensive treatment, which is considered later (Solomon and CCG results).

Based on a summary of the literature by Hinrichsen, 1939

daily later 3 times a week for considerable periods. Intelligent patients have insisted that they experienced improvement in visual acuity even though fields remained unchanged under B_1 B complex, and A vitamin therapy We have observed field improvement in one case in which atrophic change seemed to have come to a standstill on thiamine chloride intravenously but such interpretations are risky If and when a general arsenic eliminant becomes available ocular complications will probably respond to a degree proportionate to the promptitude of their recognition.

Results from Tryparsamide Therapy —In spite of the obvious difficulties in evaluating a question of this sort we have in Fig. 778 prepared a tabular condensation from Hinrichsen s paper (1939) to summarize a group of carefully controlled series and resumés in which the tabular classification was applicable to the data given While such comparisons, lacking a standard of

agreement as to what shall constitute complete and partial remission and within the limits of elapsed time, cannot be completely satisfactory it is apparent that in its chief field of effectiveness, namely general paralysis, the drug is capable of securing complete remission with economic rehabilitation in approximately one half of the early cases remission in one fourth of the later cases.

Aldarsone as Substitute for Tryparsamide.—Previously described in Chapter VII, this drug, a pentavalent arsenical synthesized by Raiziss and coworkers, has according to the observations of Kamman (1938) and Spiegel, Leifer and Sarason (1941), totalling 186 cases, practically no complications of any sort, including ocular damage, and the drug was used with actual improvement in patients whose fields showed contraction. The serologic and clinical results were promising and deserve further study especially when tryparsamide is contraindicated.

Results of Fever Therapy in General Paresis (Induced Malaria and Artificial Fever).—The statement of the accomplishments of pyrexial therapy in this field can now be reduced to quite definite percentages, thanks to the shake-downs in definition and interpretation produced by the long experience of a number of individual observers plus the evaluations of such groups as the Committee on Non-Specific Therapy of Syphilis sponsored by the United States Public Health Service. Best expressed in the words of this group (J.A.M.A., 115 677 1940) are the now generally accepted terms for outcome, as follows

The term paresis in this study refers to the symptom complex caused by syphilitic meningo-encephalitis, characterized by distinctive psychiatric, neurologic, serologic and spinal fluid abnormalities.

All patients were classified by degree of involvement on beginning treatment with fever therapy The following subdivisions were maintained throughout the evaluation:

( ) Mild: Relatively free from signs of deterioration, with mental symptoms, usually transitory

(b) Intermediate Symptoms of manic excitement, depression or other psychiatric syndromes, in addition to evidence of moderate deterioration

(c) Severe: Evidence of advanced deterioration.

The clinical results of therapy were defined as:

(a) Remission Sufficient clinical recovery to permit the patient to return to his former socio-economic status.

(b) Improved: Complete or partial disappearance of clinical manifestations without corresponding improvement in the capacity to return to the former socio-economic status.

( ) Unimproved: N detectable clinical evidence of change in the course of the disease.

(d) Progressed Clinical condition less satisfactory after therapy than before.

(e) Death: Treatment deaths during therapy or deaths regardless of cause, occurring during or within three months subsequent to therapy

Occasionally further grouping of the cases in terms of clinical results was necessary in order to effect additional comparisons. These groups were

(a) Clinical success: Remission.

(b) Clinical failure· Unimproved, progressed, death.

(c) Relapse: Reversal from clinically successful result to clinical failure.

The serologic results of therapy as determined by spinal fluid and blood tests, were classed as·

( ) Positive (which includes cases with doubtful reactions).

(b) Negative.

(c) Not done.

The various degrees of abnormality of the spinal fluids were classed as Groups I, II and III previously described (p. 120).

Figure 779 presents the clinical results of malaria and artificial fever in the three grades of clinical paresis. Throughout the table artificial fever has somewhat the advantage in remissions secured (58 per cent malarial *versus* 59 per cent artificial in mild cases for example) The differences we are inclined to believe are within the margin of error due to material, selection and interpretation and *do not conclusively prove superiorities or deficiencies.* The mortality figures, however also favor artificial fever

Ewalt and Ebaugh (1941) directed attention to this interpretative factor in statistical material, and rated an intensive fever therapy-chemotherapy routine as beneficial to from 60 to 70 per cent of patients with paresis.

Figure 780 brings Fig 155 p 345 up to date for the purpose of showing again the shake-down to a range of 25 to 35 per cent of good remissions to be expected of malarial therapy with improvement in 25 to 40 per cent.

Fig 779

CLINICAL RESULTS AFTER THIRD YEAR IN PATIENTS UNDER TREATMENT OBSERVATION THREE OR MORE YEARS*

Method of Fever Therapy	Remission. Number	Remission. Per cent.	Improved. Number	Improved. Per cent.	Unimproved. Number.	Unimproved. Per cent.	Progressed. Number	Progressed. Per cent.	Death. Number.	Death. Per cent.	Total. Number.	Total. Per cent.
Mild Paresis												
Malaria	67	[illegible]	[illegible]	21 [illegible]	16	7 [illegible]	6	[illegible]	9	[illegible]	[illegible]	[illegible]
Artificial fever	[illegible]	[illegible]	10	[illegible]	6	11 1	4	7 4	[illegible]	[illegible]	[illegible]	[illegible]
Intermediate Paresis												
Malaria	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	15 7	[illegible]	[illegible]	[illegible]	11 [illegible]	[illegible]	[illegible]
Artificial fever	[illegible]	[illegible]	40	41 7	14	14 [illegible]	[illegible]	[illegible]	10	[illegible]	[illegible]	[illegible]
Severe Paresis												
Malaria	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Artificial fever	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	14	[illegible]	[illegible]	[illegible]

* Including treatment deaths and deaths within three months of treatment.
From J A M A [illegible]

The duration and degree of fever necessary to obtain such results as the Committee reports is given on p 345 Kopp and Solomon (1939) in a one- to thirteen year observation material (309 cases, 189 with general paresis) found that significant statistical differences did not exist between the groups reaching levels of 104 105 and 106 degrees with respect to clinical results The best results were obtained when more than 150 hours at 100° F were experienced Less than 10 paroxysms were definitely less effective than more than 10 The frequency of paroxysms and length of malarial incubation period made no difference

Serological Effect of Malarial and Artificial Fever Therapy—It is now quite generally accepted that clinical improvement and serological improvement under fever therapy in general, and in fact under all the indirect or systemic methods of treating neurosyphilis, do not necessarily go hand in hand (see above)

According to Hinton and Blalock, the cell count of the spinal fluid following fever therapy is the first factor to show improvement and the colloidal test is particularly resistant in the first two years Thereafter however the ultimate proportion of negative colloidal tests is larger

than of any of the other reactions, the Wassermann reaction on the blood being the most resistant to change and the spinal fluid Wassermann reaction intermediate between the two. Osborne estimates that the maximum improvement will be established between the second and the fourth years. O'Leary and Brunsting, examining the status of patients three to five years after treatment, found the spinal fluid completely negative in 58 per cent of 60 cases, and markedly improved *in an additional 20 per cent. Of 36 patients who had been in complete remission*, 73 per cent had attained completely negative reactions i the blood and spinal fluid. In the taboparetic as distinguished from the paretic group, the results were less satisfactory Osborne reported negative blood Wassermann reactions in 35 per cent and negative spinal fluids in 29 per cent of approximately 400 mixed cases of neurosyphilis. Hinsie and Blalock, in 197 patients treated with malaria between 1923 and 1928, some in combination with tryparsamide, and evaluated in 1932, found 78 per cent had obtained negative blood Wassermann reactions

Fig. 780.

RESULTS IN MALARIAL THERAPY OF PARESIS

Reported by	Total Number Cases.	Complete remission per cent.	"Better per cent.	*Improved* per cent.
Aslgaard		36.0		29.0
Nonne		10.3		24.3
Lewis		31.0		
Grant nd Sylvester		26.2		
Cald ell	307	29.7		13.9
Leroy *et al.*	102	30.0		12.0
Carlson	200		48.6	
Kasche	303		35.0	
Wile nd Hand			38.9	
Freeman *et al.*	185	31.6		30.0
Schiller	722		40.0	
Crawford	26	27.0		34.0
Solomon and Epstein (other treatment and malaria)	173		63.5	
Mays, Oden and Cox	238		61.0	
Matthews, Bookhammer and Idar (malaria and tryparsamide)	511	21.6		46.3
Brown, malaria			33.0	
untreated			4.3	
QUARTAN				
Fong	436		47.0	
Kroll	62	30.0		60.0
Mays, Oden and Cox	37		78	

and 83.1 per cent negative spinal fluid Wassermann reactions. The colloidal gold curve was negative in 69.7 per cent of these patients. They could recognize no close parallelism between the clinical and the laboratory status of their cases. According to later paper by Blalock and Hinsie (1936) in paresis, the best serologic results occurred if the patient received fever therapy followed by chemotherapy but Kierland, O'Leary and Vandorea (1942) found intraspinal ther apy the most effective means of reversing the spinal fluid in all forms of symptomatic neurosyphilis. Malaria therapy however proved most effective in obtaining marked clinical improvement and in preventing progression.

It is evident, then, that while a return to serological normality may be expected in a rather large proportion of malarially treated patients, serological normal'ty is neither a prompt, a necessary nor a significant concomitant of clinical improvement. While in general it is desirable to attain

it, present knowledge of its significance is hardly sufficient to allow us to overstress it.

Comparisons of Tryparsamide and Fever and Other Methods.—Here again, tabular summaries best present the evidence for the current conclusions (*Figs* 781 782, 783)

Fig 781

EFFECTIVENESS OF MALARIA AND TRYPARSAMIDE VERSUS TRYPARSAMIDE ALONE IN PARESIS (314 CASES)*

Method.	Remission.	Markedly Improved.	Improved	Unimproved.	Total cases.
Malaria and Tryparsamide	30 (21%)	35 (24 5%)	34 (23 8%)	44 (30 7%)	143
Tryparsamide alone	32 (18 7%)	24 (14%)	29 (17%)	86 (50 3%)	171

From Matthews, Bockhammer and Isler (1938) data.

Fig. 782.

RESPONSE OF NEUROSYPHILIS TO VARIOUS METHODS OF TREATMENT*
Cooperative Clinical Group Results

	Type of neurosyphilis.					
	Tabes dorsalis.	Paresis.	Tabo-paresis.	Meningeal	Meningo-vascular	Vascular
Number of cases	985	374	149	177	281	102
Percentage of total cases	48	19	7	9	14	5
	Per cent.					
Clinical results:						
Marked improvement (total)	21	38	23	74	45	25
With spinal fluid reversal	27	48	26	84	55	38
Without spinal fluid reversal	18	33	25	48	30	21
Died or progressed (total)	15	21	23	6	11	17
With spinal fluid reversal	11	10	8	2	6	0
Without spinal fluid reversal	16	22	27	18	19	23
Methods of treatment:						
Spinal fluid reversal after—						
Routine only	29	11	17	57	43	45
Routine plus intraspinal	49	18	28	62	50	45
Routine plus malaria	22	9	12	†27	10	†10
Routine plus tryparsamide	40	17	†46	†18	47	†30
Marked improvement after—						
Intraspinal (total)	25	48	24	70	47	38
Malaria (total)	22	43	34	65	46	†19
Tryparsamide (total)	24	37	21	65	45	23
Routine only	15	16	14	78	38	10
Routine plus intraspinal	23	33	22	71	40	43
Routine plus malaria	14	36	†31	†88	†50	†13
Routine plus tryparsamide	16	20	†7	†60	44	—

From *Kierland, O'Leary and Vandoren, Ven. Dis. Inform.* 23 360, 1942.

† Percentages based on total of less than 20 cases.

The results from Solomon's clinic at the Boston Psychopathic Hospital (Kopp, 1942) are presented because they represent probably one of the most extended and prolonged experiences with tryparsamide in the literature.

Fig. 783.

CLINICAL STATUS OF PARETIC PATIENTS FOLLOWING DIFFERENT MODES OF TREATMENT AT BOSTON PSYCHOPATHIC HOSPITAL

Therapy	Malaria.	Mechanotherapy	Tryparsamide.
Number of patients	173	118	81
Observation	3–9 yrs.	½–7 yrs.	2–15 yrs.
Arrested	48.5%	7.9%	42.0%
Improved	15.2%	40.7%	29.6%
Unimproved or worse	13.8%	34.6%	11.1%
Death (all deaths)	22.5%	16.9%	17.3%
Due to general paralysis.	14.5%	8.5%	6.2%
Due to treatment	2.3%	2.5%	

Relative Response of Various Types of Paresis.—In Fig. 784 quoted *from Hinsie and Blalock are summarized the outcomes of various types of* paresis under exclusive malarial or tryparsamide therapy and combinations of the two. As in the literature in general it is apparent that expansive types make the best response, and that euphoria and grandiosity argue a favorable rather than an unfavorable outcome.

Fig. 784.

THE PROGNOSIS OF INDIVIDUAL TYPES OF GENERAL PARESIS UNDER MALARIA, TRYPARSAMIDE OR BOTH

(Quoted from Hinsie and Blalock, 197 cases, four to seven years after treatment.)

Outcome.	Manic per cent.	Expansive per cent.	Simple dementing per cent.	Schizophrenic.
Remission	19	37	18	4.2
Improved	0	13	14.5	33.3
Unimproved	24	19.5	21.5	25.0
Dead	57	30.5	46.0	37.5

General Comparative Summary.—The situation, then, we think, may be *summarized approximately in these terms, which no doubt will not please* the enthusiasts on either side. The choice of mode of treatment must be individual, not routine. The general situation may perhaps best be defined by saying that the young, robust paretic or preparetic with definite though

early symptoms or signs, who can afford hospitalization who is likely to become uncontrollable under ambulatory conditions if the process is stirred up by any form of treatment who must rapidly achieve a result before his own funds or those of his backers are exhausted or who is approaching the age of increasing risk (say forty-five years and over) is wisest to take malarial therapy as a first choice. On the other hand there does not seem at the moment, in view of the excellent tryparsamide results reported and the steadily decreasing risk of eye complications under better technical management, particularly strong reason why asymptomatic neurosyphilis, even with a preparetic or "red flag" formula should be subjected forthwith on recognition to fever therapy Particularly does the method seem inappropriate in such a situation when unsupported by general systemic treatment though the same statement applies to tryparsamide Six months or a year's trial of tryparsamide, or even two years of tryparsamide can frequently be carried by these patients without difficulty or embarrassment, while they remain at work as effective members of the community Where age debility and nonsyphilitic complications and contraindications to malaria are factors, tryparsamide also deserves first choice. With the growing comprehension of the advantages and possibilities of combined treatment precedence may remain an issue for decision but exclusion will tend to disappear

The important rôle played by chemotherapy in conjunction with all forms of fever and especially tryparsamide therapy is brought out by Simpson, Kendell and Rose's critical review of the larger part of existing material (1942) It is further emphasized in a somewhat unexpected fashion, by Solomon and Epstein's report (1036) of the tryparsamide-induced fever sequence, which our own limited observation confirms that malaria after prolonged use of tryparsamide without reversal of serologic findings, results in a sudden and surprising drop to normal. Evidently there is an effect of preparation for a good fever result, produced by preliminary chemotherapy as well as an accentuation of chemotherapeutic effect by fever

Postmalarial Use of Mapharsen.—Dattner and Thomas (1942) have carried over with intensification the Viennese practice of employing a trivalent arsenical after malaria, using mapharsen instead of neoarsphenamine, believing that the literature does not support the superiority of the pentavalent arsenicals as postfever routine They administer 10 daily intravenous injections of mapharsen, 60 milligrams each immediately following the last malarial fever The spinal fluids were not examined until six months later and the results have been stated to be satisfactory They do not approve the prolonged use of any arsenical after fever and do not continue routine weekly injections for more than six months, unless the fluid shows increased cells and protein at the end of this time

What then, in General May Be Expected of Existing Forms of Treatment?

1 Malaria and induced fever run neck and neck, with slight advantage to induced fever in early cases and a lower mortality in severe cases.

2. Intraspinal therapy produces the better serologic results, malaria the better clinical results and malaria is the better preventive of progression.

3. Tryparsamide, prolonged, can practically equal malaria, in paresis.

4 Fever and tryparsamide, employed as early as possible is the treatment of choice in the vast majority of cases.

5. Routine intravenous and intramuscular therapy still holds a place in tabes and as a brief preparation for more resistant (paretic) neurosyphilis.

Treatment Combinations in Neurosyphilotherapy

It must be apparent that from the various methods described, an almost unlimited number of commutations and permutations designed to meet individual indications can be devised. This individualization is eminently desirable up to a certain point, but thoroughly confusing where other than expert guidance must be relied on. We have accordingly in Fig 785 skeleton ized the situation for American practice at the time of this revision, omitting mention of methods exclusively used abroad or those still in their experimental stages, except in dealing with the difficult problem of special symptoms.

Treatment of Special Groups of Cases, Types, and Symptoms

Response of Individual Symptoms to Standard Treatment.—For purposes of comparison and review the general symptomatology of neurosyphilis as shown in Fig 750 should be compared with the percentage of good clinical responses secured by standard methods, including intraspinal therapy as shown in Fig 768. It will be apparent that the frequency of a symptom is by no means closely coordinated with its susceptibility to relief by treatment.

Furthermore there is an element of uncertainty at the outset as to whether a patient will fall into the category of easy arrest with routine standard treat ment symptomatic without corresponding serologic response easy serologic response with inadequate symptomatic relief temporary response with easy relapse of symptoms, serology or signs or progression in spite of or following treatment, with or without negative serologic signs, initially or as a result of treatment. The effort to clarify these often puzzling situations has been made by such authors as O'Leary using the CCG material, and Dattner and Thomas using the Bellevue Hospital material. Their views may well be summarized in advance of our own.

O'Leary (1936) view can be summarized as follows. He believes that response in neurosyphilis is conditioned primarily by the state of the defense mechanism, and that once routine spirillicidal types of treatment have done what they can, further progress in the individual case is determined by the responsiveness of the non-specific mechanisms. T determine whether patient has an active defense mechanism, observe the behavior under treatment. Rapid early response to mild types of treatment indicates permanent type of improvement, while clinical and serologic responses that require resort to intensive measures and supplemental therapy over period of three or four years, denote incomplete and often temporary improvement. The char acter or type of the spinal fluid is guide to intensity of the process. Low grade abnormality (as in Type I, we assume) responds more quickly than high grade abnormality (Type III). Serologic findings on the blood are untrustworthy guides t treatment in neurosyphilis. Clinical responses such as gain in weight, increased hemoglobin, decreased fatigue and irritability and improvement in memory may be more significant for an eventual good outcome, than relief of crises or pains. Treatment begun early (before the fifth year) while the patient is organizing his defense and nonappearance of spinal fluid involvement by the fifth year are both prognostically favorable circumstances. Patients who have received no previous treatment respond more rapidly and the response is more likely to be permanent than in those who have received previous treatment. The presence of intercurrent disease such as tuberculosis, nephritis, colitis etc reduces the effectiveness of treatment. On the other hand complications of syphilis such as cardiovascular disease and osseous syphilis do not influence the results of treatment unless they interfere with the use of intensive methods. The value of nonspecific therapy in the form of malaria or fever induced by the hypertherm or some other machine, or vaccines, lies probably in biologic changes rather than in any sterilizing effect of the fever. Accordingly the response both clinical and serologic which follows course of fever therapy is a favorable indication of an improvement in the status of the defense mechanisms.

O'Leary CCG figures supporting his contention that neurosyphilis is largely taken care of in the biologic course of the disease are worth special quotation. Thirty-three per cent of patients who had untreated neurosyphilis of less than one year duration were positive in the spinal fluid;

Fig. 785

A SCHEMA OF TREATMENT IN NEUROSYPHILIS

Number	Type.	Preparatory* unit course.	Routine† unit course.	Intensification.	Tryparsamide.	Nonspecific fever.	Special.
1	Asymptomatic meningeal and meningovascular	(1) [illegible] mercury [illegible], [illegible] to [illegible] grain, [illegible] injections weekly or (2) bismuth 10 to 20 injections every three to seven days.	Eight to 10 injections [illegible] (weekly) or 10 to 14 neoarsphenamine,‡ 1 injection every four to five days, alternating with [illegible] metal.	Three to five more units plus sodium iodide intravenously 20 to 40 injections or large doses by mouth.	Not needed.	Not needed.	Not needed.
2	Asymptomatic parenchymatous [illegible].	As in (1).	Three to five courses as above depending on response.	Sodium iodide intravenously or large doses by mouth.	Replaces arsphenamine after 2 unit courses if unresponsive.	Malaria may be given to robust young adults, 10 to 16 chills.	Intraspinal, 6 to 10 injections.
3	Asymptomatic preparetic.	Continue preparatory and first unit course.	One or two units, then examine CSF	Shift to tryparsamide or fever	(1) T[illegible] courses with mercury or bismuth (2) (preferred) weekly injections for one to two years.	Pretryparsamide malaria preferred if young and uncomplicated.	
4	Symptomatic neurorecurrence.	Succinimide mercury and iodide intravenously preferred.	Two courses and CSF examination. If not responsive give [illegible]	Three to five more units or manage as preparesis.	Only if preparesis.	Not needed unless preparesis.	Intraspinal.
	Symptomatic cerebrospinal.	Bismuth preparatory as in (1b).	Three to five unit courses.	Rarely needed. Iodide.	Only if resistant.	Rarely needed. [illegible]	Intraspinal 6 to 10 injections.
6	Symptomatic early tabes.	Mercury or bismuth with iodide as in (1).	Three to five unit courses.	Intraspinal.	If resistant.	Not especially effective and often inadvisable.	Intraspinal 5 to 15 injections.
7	Symptomatic late tabes.	Low dosage bismuth or [illegible] (oral or [illegible]).	Small dosage neoarsphenamine 6 to 15 injections.	Rarely advisable.	If resistant.	Rarely advisable.	Chronic eliminative, dietary, anti-infection.
	Optic atrophy	Small dosage, bismuth 10 injections.	Bismuth preferred.		Contraindicated.	Malaria probably more effective than intraspinal.	Swift-Ellis valuable method.
	Gastric crises.	All methods equally uncertain. For suggestions see text.					

* See Fig. 783. † See Fig. 784. ‡ The status of [illegible] and [illegible] is as yet undetermined.

Fig. 785 (Continued)

A SCHEMA OF TREATMENT IN NEUROSYPHILIS (Continued)

Number	Type.	Preparatory* unit course.	Routine† unit course.	Intensification.	Tryparsamide.	Nonspecific fever	Special.
10	Early paresis, uncomplicated.	Combine preparatory with first unit course.	One to two units if no urgent indications for immediate fever		Follow malaria.	Malaria first preferred.	
11	Active paresis.	None or one course.	None, or 1 unit if tryparsamide used.		Follow malaria if no contraindication.	Malaria first always unless unobtainable or contraindicated.	
12	Deteriorated late paresis.	Preparatory treatment for supposed purposes.	One to two units may precede or follow malaria.		Precede or follow malaria.	Malaria or milder measures if not contraindicated.	
13	Complicated paresis.	One course.	Two units.		If not contraindicated.	Depends on case and complications.	
14	Vascular neurosyphilis.	Bismuth or mercury and iodide.	Small dosage arsphenamine or avoid entirely		Useless.	Dangerous.	
15	Local inflammatory lesions.	Mercury and iodide or bismuth, as in ( ).	Two to three unit courses.	Iodide by mouth and intravenously	Only if serology demands.	Rarely needed.	Intraspinal or intracisternal.

* See Fig. 783. † See Fig. 784.

through repeated sieges of lightning pains and the overload on his excretory and defense mechanism which can be produced by dental foci, for example, which are scarcely detectable by the roentgen-ray. We have repeatedly seen the chase for a focus of infection with successive periods of temporary relief following each new discovery and removal, run the gamut of a roentgenologically-negative and dentally-approved molar, a foreign body in the upper jaw, a chronically infected prostate, a fistula in ano, and an atonic infected colon. It is wise, therefore, not to permit dental expediency and the limitations of roentgen-ray visualization to allow the tabetic to retain devitalized and suspicious teeth. Infected tonsils have seemed even less directly responsible for trouble. Colonic irrigation, though easily overdone, and a carefully selected diet, low particularly on the carbohydrate side, assist in the control of intestinal infection. Flooding the patient with well-soured milk (at least 3 pints daily) between meals as in dealing with the Kendall syndrome of intestinal carbohydrate intolerance may be helpful. The lowering of the pH of the intestinal tract by dilute hydrochloric acid by mouth, and at times the intestinal antiseptic virtues of mercury with chalk deserve more or less empirical trial. Plying the patient with mineral oil which leeches him of his provitamin A, and routinized cathartieism are poor substitutes for good judgment. In the atonic intestinal disturbances of the tabetic in which the gut seems to act as a focus for lightning pain etc., the vitamin B complex is especially useful.

Care of the Urinary System.—One of the first duties of the physician when a tabetic comes under medical care is to inquire into renal and bladder function. The blood urea nitrogen content, phenolphthalein functional tests, examination of the urine for evidences of infection, and an estimation of the degree of urinary retention are minimal requirements. "Every tabetic is a potential uremic" is a maxim that should be constantly kept in mind. In all but the earliest and mildest cases, catheterization of the bladder may be required, and this should be undertaken only with the most rigid precautions against infection, and should never be performed except by an expert urologist if the patient has been leaking and dribbling for some time and undergone thereby definite renal functional impairment. The catheterization of such a bladder precisely as in retention due to prostatic hypertrophy may precipitate the patient, without warning, into uremic coma.

The symptomatic inquiry in these patients is important. Slight signs of involvement of the mechanism of the bladder include dribbling, difficulty in starting the stream, difficulty in stopping, nocturnal bedwetting. It is unpardonable for the physician to catheterize repeatedly any patient without at least a survey for signs of neurosyphilis. Even postpartum retention may have sometimes a tabetic and not an obstetrical origin. It is well first of all to realize that dribbling is more apt to be a symptom of a distended and paralyzed bladder than of a deficient sphincter control. The question of whether such a distended bladder should be evacuated by catheter has no categorical answer. If the patient shows uremic symptoms or has a high blood urea, a retention catheter may be introduced and slow prolonged drainage performed as in cases of prostatic hypertrophy. In some instances suprapubic stab drainage has been life-saving. If the urine is uninfected (no pus or bacteria) and the renal function and blood urea are normal catheterization, even to obtain an exact phenolsulphonephthalein return may well be avoided. If expert urological consultation is available at this time catheter

drainage may be performed. On the other hand, if there is evidence of only moderate retention and no infection, the patient should be put under treatment for syphilis and systematically drilled in the evacuation of his own bladder. Most patients manage to strike a posture, as in prostatic cases, in which they can secure an evacuation. They may empty the bladder completely with the bowel movement. They may empty it in the warm bath, or at the sound of running water or with heat, cold, or pressure over the lower abdomen. In this way many patients can be trained to empty and keep the bladder uninfected and renal function normal. On the other hand, if there is evidence of marked residual urine (bladder percussed after evacuation, and so forth) catheterization by the physician with complete evacuation of the residual urine three times a week, accompanied by reeducational efforts, and treatment for neurosyphilis, often results in surprising gains. A residual urine of 22 ounces may be reduced to one-half ounce in the course of a year. If there is evidence of marked infection, appropriate irrigation of the bladder under direction of the urologist will be desirable. Every possible effort should be made to avoid introducing the patient to catheter life—although Stokes has seen at least one surprising instance of longevity under such circumstances, good health and comparatively little bladder infection 20 years after the institution of exclusive catheter evacuation.

The periodic rechecking of phenolsulphonphthalein excretion and blood urea, quite as much as the ordinary urine examination, are essential parts of the reexamination and observational control of the neurosyphilitic patient whose bladder function has once shown signs of impairment. In elderly patients the possibility of complicating prostatic hypertrophy should not be lost sight of. The success of these measures is, according to Stokes' experience with 73 cases studied with the help of the Section of Urology of the Mayo Clinic, dependent largely upon the grade of involvement when treatment is begun. Mild and moderate degrees of cord bladder show excellent and good results in approximately 70 per cent of cases. In severe grades of involvement, good results were only obtained in approximately 15 per cent. The aggregate shows 11 per cent excellent, 20 per cent good, 29 per cent fair and 40 per cent slight or no results.

A field is developing for the use of parasympathicomimetic drugs such as mecholyl in improving the function of atonic or "cord" bladders. Bauer, Lipton and Altschule (1943) especially commend "Furmethide" (SKF) for this purpose in a study controlled by cystometric measurements.

In the acute myelitic bladder paralysis, it cannot be overemphasized that the care with which catheterization is done may make all the difference between recovery and death from complicating pyelitis. In such cases hexamethylene or hexylresorcinol should be used as prophylaxis.

Libido and Potentia.—Sexual impairment in tabetics seldom makes a striking improvement, probably because of the complexity of the various factors involved in the psychic state, the neurogenous damage and acquired genito-urinary disease. In 24 per cent of Stokes and Shaffer's patients the response was good, in 21 per cent fair and in 54 per cent slight or none. Testosterone as the propionate intramuscularly (10 to 25 mg. daily) followed by methyl testosterone by mouth (30 to 40 mg. daily) may be tried. An intensive vitamin therapy by improving general health may be useful. Reassurance and psychotherapy are essential, and as in psychogenic impotence the suggestion of Owen and Wortis (1942) on conjoint use of mecholyl as in anxiety states may be tried.

Control of Paresthesias and Lightning Pains.—The control of these symptoms, while quite largely dependent upon treatment and often responsive to relatively mild measures, such as single course of bismuth or

bismuth arsphenamine sulphonate, is in the long run rather difficult matter It is in this connection as well as in the raising of the general level of well-being of the tabetic that rest, change to a warm winter climate, avoidance of overstrenuous exertion, and the occasional judicious use of mild stimulants (benzedrine) and sedatives and analgesics becomes an art. Emphasis should be placed upon the undesirable effect of making a barbiturate addict out of a tabetic whose symptoms could ordinarily be controlled by aspirin and acet phenetidin. The usefulness of alcohol as an analgesic cannot be denied in some cases, but its general effect on the tabetic in the amounts he tends to use it, is not good Hard liquor which gives him the most relief is particularly undesirable the glass of sherry after dinner often a valuable sedative Occasional courses of colon irrigation a dose of castor oil careful instruction in anticonstipation regimen irradiation with ultraviolet light, and sheer encouraging talk, play their part from widely varying angles. The physician in charge of such a patient should not depend too exclusively on antisyphilitic measures but should first carefully canvass the field of possible causes and nonspecific methods of relief The vitamin therapy of tabes has been discussed on p. 1010 in conjunction with vitamin deficiency aspects. Thiamine chloride alone is of little use in lightning pains, but the B complex in large doses of an active preparation is of undoubted service, partly perhaps by its effect on a bowel infection focus and atonic constipation A patient seen jointly by Stokes and Moore believed calcium pantothenate and the pyridoxin fraction were most effective to judge by experiments on himself When antisyphilitic measures are resorted to for this group of symptoms, especially in the sallow cachectic, and debilitated patient, a tonic procedure as distinguished from a treatment for arrest is often indicated The essentials of tonic therapy include small doses of neoarsphenamine (0 45 Gm once a week for six to ten weeks), mapharsen (0 04 to 0 06 Gm once a week for six to ten weeks) or bismuth arsphenamine sulphonate (0 1 Gm intramuscularly every fourth day for 15 to 20 injections) Several such courses at intervals of three or four months may be sufficient to place the tabetic "wreck" on his feet and maintain him in reasonable comfort for a long period

The adoption of fever therapy should be carefully weighed with consultation if possible Early in the course of a tabes fever therapy may be quite effective, but the furious exacerbations that accompany the fever bouts may be uncontrollable and unendurable, and force discontinuance of the treatment. Neurosurgical measures (cordotomy) are for desperate situations only and avail little or hasten the end

The Casual Use of Morphine for the Relief of Any of the Painful Symptoms of Tabes, Including Crises, Cannot Be too Vigorously Condemned.—This is one of the most unfortunate residua of old-school medical practice The combination of tabes and morphinism is a therapeutically impossible one and inevitably leads to deterioration The impulse to give a hypodermic for the relief of pain should be drilled out of instead of into medical students. Morphine is only rarely a necessity in dealing with the painful complications of neurosyphilis if the methods of procedure here described be given their proper place

Salicylates and other coal tar derivatives are useful and usually adequate even in dealing with the typical "shower or exacerbation of lancinating pains An excellent prescription includes 5 grains each of acetphenetidin and acetylsalicylic acid and 5 grains of sodium bromide in powder or tablets

Certain of the proprietaries are excellent, and the barbital derivatives may be administered at the same time for their sedative and anxiety reducing effects. A shower of lightning pains, like a gastric crisis, may occasionally be stopped abruptly by an intramuscular injection of 10 to 15 minims of one to one thousand epinephrine solution (Sicard and Lermoyez) Heat is usually not welcome, though some patients may obtain relief in the hot bath. The close connection between pains and stasis conditions in the gastro-intestinal tract is evidenced by the quick response in many cases to a cathartic. Intercurrent infections should be sedulously avoided where possible by patients subject to lightning pains. Exposure to ultraviolet light in moderate doses is helpful.

The more radical procedure of Rajka and Radnai, involving sharp repeated erythema doses ith intramuscular injections of the patient own whole blood, may be employed. Not more than 30 lamp exposures and 60 whole-blood injections divided into two courses should be given, the blood being drawn half an hour after the lamp exposure (10 cc.) and the quartz lamp exposures being given three times ek. This method, however, is still in the experimental stage, though we have known its less intensive use to be followed by marked benefit. Periarterial sympathectomy has been without effect.

By standard methods of treatment lightning pains respond with excellent results in 16 per cent, good results in 31 per cent, and fair results in 26 per cent, aggregating 73 per cent improvement. The notorious persistence of this symptom after the apparent arrest of the degenerative process, and the achievement of serological negativity is a particularly trying feature of late tabes. Intraspinal introduction of lipiodol recommended by Forestier (1935) has not been fully evaluated and we have had no experience with it. Neurosurgery in the form of cordotomy is a last resort indeed, and in our observation more often leaves a deplorable wreck than a materially benefited patient. Kahn and Barney (1937) however report superior results with anterolateral cordotomy For the obstinate case free from other contraindications, malarial therapy may be considered but in the so-called "burned-out" type is rated by Sterner as ineffective. The presence of an infected genito-urinary tract is regarded by most observers, particularly Moore, as a sharp contraindication to the attempt to deal with late tabetic symptoms by malarial therapy Ebaugh Schamberg and Greenbaum and particularly Ebaugh had, in contrast to the discouraging Continental results (Dreyfus) approximately 30 per cent im provement in lancinating pains following the malarial siege. Wile obtained general symptomatic improvement in 53 per cent, increased to 67 per cent on observation, but mentions no symptoms specifically Hot baths seemed to Mehrtens and Pouppirt particularly effective in dealing with lancinating pains.

Treatment of Ataxia.—The treatment of such a symptom is, of course dependent upon the cause. The spastic ataxic case seems, in our experience, to be made worse at times by the use of arsphenamine and obtains little relief from other forms of treatment. The tabetic type likewise gives a low proportion of lasting good results with standard treatment, only 5 per cent in the aggregate being rated excellent, 16 per cent good, 28 per cent fair and 51 per cent slight or none. The acute early types in comparatively young patients may however be transformed by treatment. In six months they may change from a state in which they can barely flop about the office, to one in which they walk so well that they are not recognized by their friends. A careful iodide and mercury preparation without too early use of arsphenamine has seemed

to us to contribute to this good result, and the impulse to employ malaria should not necessarily be substituted for it. The tabetic ataxic patient responds to fever therapy according to Steiner (mild cases) Ebaugh, and Wile. If no response has been secured in one to two years of standard treatment, including tryparsamide when serologically indicated, malarial therapy may be tried. Moore's patients, however were made worse by it.

The tabetic ataxic patient who fails to respond can be taught to substitute his eyesight for his sense of motion and position, and to practice muscle reeducation and balance by drill in placing his feet on painted foot marks, looking at them or keeping them "in the corner of his eye" as he walks. This reeducation of the tabetic was developed to its fullest extent by Fraenkel through systematic gymnastic training. The psychic factor in ataxia is quite apparent to any considerable experience and reassurance plays no small part in recovery of control. The patient who flounders in one's presence may make a much better showing in a crowded street, where he loses his self-consciousness. Patients with marked ataxia should not in general be subjected to avoidable spinal puncture, for in occasional cases there seems to be increased difficulty afterwards.

Treatment of Gastric Crises.—This commonest form of visceral crisis presents a discouraging but by no means hopeless therapeutic problem. With standard methods of treatment marked amelioration of symptoms is possible in 24 per cent, the usual response consisting in a reduction in severity and length of attacks with or without an increase of intervals between them. This degree of relief may restore an incapacitated person to self-support. The addition of tryparsamide in resistant cases slightly increases the good result. Fever therapy and especially malaria often afford striking temporary relief and the response may even be prolonged. There are no clear-cut indications or contraindications for it other than those generally applicable to the use of fever therapy in tabes, and the method is essentially one of trial and error following the failure of simpler and less hazardous methods. McGrath, Rudolf Driver Gammel and Karnosh, and Ebaugh, report relief in cases previously subjected to prolonged treatment by other methods.

The Cooperative Clinical Group results are more encouraging—48 per cent of patients completely relieved, an additional 23 per cent benefited. Routine standard treatment was more effective than fever and tryparsamide or intraspinal methods.

The combating of the neurosis, the panic, fear and hopelessness which seem to be a psychic accompaniment of gastric crises is often as difficult as any phase of the treatment. Here, too the cardinal error of the profession is the administration of morphine. As Steiner says most patients thus treated die of their addiction rather than their disease. If the practicing physician could be induced never to give a hypodermic injection of morphine for abdominal pain until he had noted the pupillary reactions and knee-jerks there would be an improvement worth while in the outlook of the average patient with gastric crises.

Symptomatic relief in the attack may be secured in the following varied and sometimes surprising ways. Simons (1930) has compiled most of the literature on this subject.

Bending the standing patient backward over the foot of his bed until his feet fly from the floor has been know to stop an attack. Intramuscular injection of epinephrine will stop some cases. Magnesium sulphat intramuscularly 5 cc. of 20 per cent sterile solution. Il quiet the patient temporarily nd Marinesco, Sager and Façon employ the drug intraspinally 1 to 2 cc of a 25 per cent solution. Recall the risk of magnesium poisoning, and have calcium gluconat t hand.

The most widely recommended method (Simons, 1930) is that developed on the Mayo Clinic service by McFarland (1923) consisting of the intrarectal use of 40 grains each of chloral and sodium bromide in an ounce of water If the room be darkened and the buttocks of the patient elevated, relief follows in few minutes even in quite severe cases, and in an hour the patient may fall asleep. In 75 per cent of cases the response lasted two to five hours. No habituation develops and solution of the two drugs may even be given to the intelligent patient for self administration. On one occasion chloral delirium developed, but disappeared on suspension of the drug. Alajouanine and Horowitz (1932) found atropine sulphate, intravenously in 1 to 3 mg. doses, effective in 30 cases. In 2 morphine addicts this treatment failed. Other drugs recommended include: sodium and potassium nitrit orally (Bouchard) 1 drop of tincture of iodine, in 15 cc. water every thirty minutes to check the vomiting (Holmes) alkalies or hydrochloric acid, depending on the gastric acidity· sodium luminal 0.3 Gm. in saline solution intravenously (Farnell, 1936); hypertonic glucose intravenously (25 per cent solution, 10 cc. every two days) (Farago, 1930)· hypertonic saline solution (Alajouanine *et al.*, 1930); 5 to 10 units of insulin, typhoid vaccine dissolved in neoarsphenamine and given intravenously; octinum (Nagel, 1937); various drugs including cerium oxalate, extract of cannabis indica, chloroform codeine and cocaine by mouth. Snake venom may be tried. Simons (1930) suggests 0 015 to 0.03 Gm. phenobarbital three times day for its effect on the patient morale.

Measures directed to the stomach are usually ineffective, though repeated washing sometimes shortens the attack, especially if there is evidence of gastric distention. Intravertebral injection of the splanchnic nerves ith 0.5 per cent cocaine solution was relatively ineffective, is inaccessible, and has been rated by Steiner and ourselves as of little avail.

Dehydration and acidosis must be dealt with by subcutaneous and intravenous administration of fluids, glucose, etc.

The surgical treatment of gastric crises is still in the experimental stage. Wertheimer Foerster and others, have sectioned the dorsal communicating branches of the posterior root, sometimes with good and sometimes with no results. Section of the lateral spinothalamic tract has relieved some patients. Section of the vagi is dangerous, owing to the anesthesia of the larynx. Resection of the celiac ganglion and Sicard-Robineau cordotomy (cutting of Gower' bundles and the lateral tracts of the posterior column) are as yet unaccepted methods. The whole surgical field for relief in gastric crises is at best matter of last and desperate resort.

The victim of gastric crises must be systematically encouraged to mak up the weight loss which occurs during an attack for only in this way can he be kept far enough ahead of the threatening cachexia and exhaustion for treatment to take ultimate effect. He should be told that his stomach trouble has nothing to do with his stomach, that he must gorge himself with food just short of dyspepsia in the intervals between attacks, the most nourishing foods being taken in bundance. I occasional cases in which the crisis becomes an almost continual affair of morning vomiting, feeding with the duodenal tube during the free interval of the day has produced gain in weight sufficient to turn the tide for the time being. Attacks may be brought on by nervous strain and by both intravenous arsphenamine injection, lumbar puncture, and intraspinal and fever therapy

The vitamin therapy of gastric crises is that of tabes in general (see above) Thiamine chloride intravenously or intraspinally in conjunction with wheat germ oil by mouth (Stone, 1942) should be added to the list of trial possibilities.

Other forms of visceral crisis must be dealt with by the same general methods. The laryngeal crisis should, if possible, be managed in hospital, on account of the danger of asphyxia, especially hen treatment for syphilis is begun.

Management of Primary Optic Atrophy.—Management in this condition is too often practically the only applicable term Primary optic atrophy is fortunately relatively uncommon with the inevitable disadvantage that few bservers have had the opportunity of studying and treating more than a very limited number of cases. When thus viewed from the isolated case standpoint, it must be said that practically all favorable or quasi favorable results can be matched with failure or rapid decline in vision or even an actual disaster following the use of what appear to be identical methods of treatment.

It has become increasingly clear that little but conflict of opinion develops from the publication of statistically nadequate material and small groups of cases, or the use of the "I had a case basis for reaching conclusions about the

treatment or outcome of primary optic atrophy. For this reason the publications of Moore and his associates on this subject are specially to be commended and have practically replaced in the minds of experts, a vast and heterogeneous mass of previous literature. On the other hand, it cannot be said as was pointed out in connection with the discussion of prognosis in neurosyphilis in general, that no individual judgment need be exercised about a particular case or that any one method is as yet so good as to exclude or even invariably to take precedence over all others as witness the reversal within a decade, of the Moore group's own views on the relative merits of intraspinal therapy and malaria. In dealing with small numbers of cases, a "run" of bad luck or poor results from unknown causes may reverse without justification in the long run some very positive but premature decisions. It seems wisest here therefore to quote the conclusions of Moore's group in an admirable summary at about the midpoint of their experience with the problem (Moore, Woods Hopkins and Sloan J.A.M.A. 111 385 1938) and to say that the enlargement of their case material from 191 patients to 250 cases (Moore Hahn Woods and Sloan 1942) has not apparently resulted in any other change than a more complete espousal of malarial therapy as the method of choice and a rejection of their form of intraspinal Swift Ellis therapy as involving too great risks of loss of vision. With the median type of statement allowing both methods their place, our experience is more in accord.

1 Untreated primary optic atrophy always becomes bilateral and leads to permanent and complete blindness in practically every instance within 7 years after the onset of symptoms.

"2. Inadequate routine antisyphilitic therapy apparently neither hastens, delays nor prevents the development of blindness.

"3. Adequate routine antisyphilitic therapy seems to delay the development of blindness to some extent and permanently to arrest the atrophic process in an occasional case.

4. Subdural treatment by the Swift-Ellis technic brings about permanent arrest of optic atrophy in about half the patients adequately treated, though it carries a risk of sudden extinguishment of vision in about 10 per cent of those treated. The observation periods in arrested cases ranges from 2 to 20 years.

5. Malaria therapy brings about permanent arrest of optic atrophy even more frequently (in our small material, apparently in about 85 per cent) and for observation periods ranging from 1 to 9 years.

"6. If treatment is begun while optic atrophy is unilateral, involvement of the normal eye may be prevented in a high proportion (in our material 70 per cent) of cases.

"7 The initial form of treatment of syphilitic primary optic atrophy should be induced malaria because its observed results are superior to and it is less dangerous to vision than subdural treatment. If visual failure progresses in spite of malaria, subdural treatment should always be tried. Either of these special forms of treatment should be followed by intensive and prolonged routine antisyphilitic treatment with trivalent arsenical drugs, bismuth compounds and mercury

In an earlier publication Moore suggested as a prognostic guide vision of 20/40 in the better eye as offering a favorable prognosis in about 44 per cent by intraspinal therapy

The CCG (O'Leary *et al.* 1938) found 13 per cent of patients with primary optic atrophy experiencing improvement in vision and progressive loss of vision arrested in 36 per cent. There were fewer cases of loss of vision after malarial therapy than after any of the other therapeutic procedures, perhaps because the patients received much routine therapy prior to the fever. Intraspinal therapy was the next most effective method.

Moore and associates, and we ourselves, consider tryparsamide absolutely contraindicated in the presence of, or in treatment for primary optic atrophy. Cady and Alvis have employed it, however even with improvement, and Lees (1937) believed the results with tryparsamide and bismuth equal to those by any other method.

Without intent to introduce anticlimax but the matter it is important to induce patients threatened with primary optic atrophy if possible, to learn Braille and if possible to prepare themselves occupationally for the complete extinction of vision. Their unpreachable optimism, however sometimes makes it difficult to secure cooperation in anticipation of *the event.*

General Management and Control of the Paretic Patient.—A few practical considerations, apart from the previously discussed syphilotherapeutic technics, are of importance in dealing with the potential or actual paretic patient. An early conference with relatives is highly desirable, and a responsible person should be kept informed step by step of the intended and actual treatment and the possibilities of complications. The patient's business affairs should at the earliest possible moment be gotten into safe hands and persuasion will sometimes secure a power of attorney where commitment might otherwise seem to be unavoidable. In general, commitment leaves a certain amount of psychic scar in a recovered patient, and injures his social and business status materially so that it should not be thoughtlessly or rashly carried out, either before or after fever therapy. Sequestration in a private hospital or sanatorium is often possible without actual legal formalities and records. Remission should be mentioned to the relatives as a possibility and they should also be warned of the probability of a flare-up of symptoms in the more excited type of case when treatment is first instituted. If excitement is very definite on first examination, hospitalization is practically unavoidable. If the patient is depressed, suicide constitutes a serious risk. Little should be said about prognosis, and this should be especially guarded if convulsive, hemiplegic or aphasic accidents have been noted or hebetude, sullenness and depression are conspicuous symptoms. The family must be warned of the risk of violent outbreaks. The excessive and indiscriminate sexual activities of the excited paretic must be controlled even to the point of sequestration. Our personal observation is in favor of a preliminary course of standard treatment before other therapeutic measures are adopted, thus, of course, provided the patient is in reasonably good condition mentally. The writers believe that this reduces the severity of therapeutic shock manifestations. The old or senile paretic is an unfavorable risk, despite the fact that expert handling of tryparsamide and fever therapy may enable an occasional case to achieve a therapeutic result.

Some Paretic After Effects.[*]—It is a matter of much importance and deserving of not a little reflection that modern methods of treating paresis produce a relatively large group of cases fitted, at least in the opinion of institutional authorities, to leave the custodial care of the institution and to be returned to family and community life. Personally we have had occasion several times to react very critically toward the judgment exercised by the *controlling authorities in this regard. There is moreover a residue of unfit* individuals, victims of psychic scar who require careful occupational placement, are a serious problem to wives, families and business associates and may require lifelong *supervision and even custodial care.*

A paretic in remission, even though fitted to take up gainful occupation, is not cured. Too often the striking symptomatic response in speech and appearance merely covers fundamental defects in the moral background and conduct mechanism which present themselves *as sometimes serious complications* when the patient takes up ordinary *life. Thus bigamous* marriages, financial difficulties, occasional crimes of violence, and peccadilloes such as dead-beat proclivities in the payment of bills, the passing of worthless checks, stinginess, chronic suspiciousness bursting out occasionally in paranoid manifestations, may all come to light to the discomfiture or actual injury of the family or social group which has received a supposedly cured paretic discharged from an institution into its midst.

Much more thought should be given to the development of an appropriate parole mechanism for paretic patients discharged after modern therapeutic procedures than has appeared in the literature or in practice thus far

CHAPTER XXI

FAMILIAL AND PRENATAL SYPHILIS ("CONGENITAL" OR "HEREDOSYPHILIS")

Even though the study of familial and prenatal syphilis has a poorer animal experimental background than any other aspect of the disease, it offers some of the most effective possibilities in modern preventive medicine. The fact that proper treatment of the syphilitic pregnant woman could virtually eliminate from practical consideration within a very few years the whole field of congenital syphilis has, for the last decade, made the attack on this aspect of the problem one of the fundamental popular approaches, if not the groundwork, of the public health movement to control this disease.

The basic psychology underlying this premise is found in the fact that (1) most communities are further advanced in their development of facilities to care for maternal and child health than they are in the management of the broader aspects of the venereal disease problem and (2) most privately supported organizations and the general public are much more willing to expend effort and funds toward the control of a disease which is innocently acquired in marriage and transmitted to the helpless and defenseless offspring before birth, than they are to contribute to the control of the more sordid aspects of this problem which too often embrace the whole field of sex behavior maladjustment at home, prostitution and sexual promiscuity.

Once progress has been made in any community or organization in the control of prenatal syphilis, it then becomes an easy matter to expand into a comprehensive program which will embrace the many public health and social implications of infectious early and symptomatic late syphilis. Within the last few years a veritable wave of premarital and prenatal examination laws directed toward the control of syphilis in the family has swept the country. The private practitioner, the obstetrician and the pediatrician have been placed in an unparalleled position of responsibility which they will live up to only after they have subjected themselves to a complete reappraisal of their knowledge of the control of syphilis in marriage, in pregnancy and in early infancy.

If, moreover, the all inclusiveness of this subject, which embraces in miniature every aspect of the disease, is fully realized, the problem of familial and prenatal syphilis assumes, for every physician confronted with it, an unusual piquancy and significance. When it is considered, that just a few treatments in the latter months of gestation will make the difference between a syphilitic and a healthy infant, that the whole problem of congenital syphilis can be largely solved by just a few weeks of competent medical supervision for this disease in late pregnancy with an adequate medical follow-up of the newborn child, it is hard to find anywhere in present day medicine a more effective demonstration of disease prevention or, in public health, a field more likely to show dramatically satisfactory results in reduction of disease incidence and prevalence in so short a period of time as in the field of congenital syphilis.

SYPHILIS AND MARRIAGE

Source of Syphilis in Marriage.—The responsibility for syphilis in marriage can be squarely placed upon antemarital sexual exposure of young men and women, and points directly to the treatment and suppression of the prostitute, toward attention to a study of the sex adjustment of the family the by-effects of the kaleidoscopic changes of present day living and the education of young men and women in the home and in the schools as the most fundamental form of attack on this problem.

Fournier found that 67 per cent of 208 women were infected by men who acquired the disease before marriage. Bulkley found that 88 per cent of his syphilitic women patients were married; Blaisdel (Boston), 79 per cent; Solomon, 76 per cent. Fournier analysis showed that 73 per cent of his syphilitic married women acquired the disease from their husbands. The Solomons, from critical examination of their experience, estimate that 80 to 90 per cent of the husbands acquired syphilis before marriage. Our own experience with a rural American clientele indicates that more than 90 per cent of sexual exposure in men is antemarital and that this is the source of familial infection. O'Leary and Williams (1940) have brought the observations on the Mayo Clinic conjugal syphilis material up to date by an examination of the records of 1175 married couples. Of the group in which one partner only was infected it was noted that three times as many men as women had the disease.

The more recent literature gives an increasing importance t the infection of the woman prior to marriage but does not invalidate the foregoing figures as to the responsibility of the male element, because of the difficulties, not to say impossibility of determining, in clinical study the importance of sex relations before marriage between those who subsequently obtain legal status. Brunet and Salberg (1939), in performing premarital examinations for syphilis on 913 women of the so-called lower middle class, found that of 796 single patients 4 per cent had had one pregnancy or more, which was usually terminated in abortion, and 6 per cent were pregnant at the time of examination. Of 500 patients who admitted sexual contact, 350 had had intercourse with their fiancés and 142 with other men. On vaginal examination it was found that only 177 (19 per cent) had intact hymens and in 736 patients bivalve specula were easily passed.

Decker (1934) found that among 576 families in which at least one marital partner had syphilis, 60 infected husbands and 96 infected wives had nonsyphilitic partners. Klingbell and Clark (1941) studying the question of conjugal syphilis in 236 couples, about equally divided between Negro and white, state that among the whites, the husband infected the wife in 30.2 per cent cases and the wif the husband in 13.1 per cent. Among the Negroes, the percentages were 33.3 per cent and 4.4 per cent respectively In 56.6 per cent of the white and 62.3 per cent of the colored it was impossible to determine which was the source. Among the white patients 38 per cent of the men and 7 per cent of the women admitted extramarital sexual intercourse and among the Negroes the percentages were 48 and 23 respectively

Infectivity in Marriage.—The transmission of syphilis in marriage is primarily dependent upon the duration of infectivity While this, as we have seen, cannot be exactly defined, a long experience has indicated that the chief danger lies in the first five years.

The general incidence of infectious relapse has been discussed in Chapter XIII. The infectiousness of semen and vaginal secretions, long considered important factors in the transmission of syphilis, has been shown, in the light of recent studies, to be relatively unimportant, except early in the course of the disease (especially at the time of menstruation in women) or in the presence of early infectious or relapsing mucous membrane lesions (Greenbaum Kats and Rule (1935) Kemp (1938) Parser (1941 1942))

Parser (1941) concludes that infectiousness through the vagina is ... at rather than continuous in syphilitic women and depends upon the presence of ... of local lesions The physiologic secretions are not infectious. Kemp studies have shown ... pallida has been demonstrated in the semen of patients with early syphilis in ... same frequency that it has been demonstrated in the other body fluids of patients w ... ia.

There is no adequate reason for persistence of the belief of the infectiousness of the semen of patients with late syphilis.

In the older literature Fournier found that 99 of 142 women (70 per cent) were infected in the first three years of their husband's disease and 26 per cent within the first year. Keyes placed the chance of infection by the untreated husband as 12 to 1 the first year, 3 to 2 the second year, 1 to 4 the third year, and practically nil the fourth and fifth years. In Strandberg's study of 230 marriages in which syphilis was present in one partner or the other it was found that only 67.8 per cent escaped all consequences in their married lives. Recurrence was seen during marriage in 20 per cent without infection of the partner. In 53 cases in which the duration of infection was unknown, 41 per cent transmitted the disease, 59 per cent did not. The disease was transmitted to the partner later than the fifth year in 20 per cent. In 2 cases transmission took place after the eighth year. In the more recent studies of O'Leary and Williams (1940) it was revealed that where the estimate of the duration of the infection was definite, very few partners were infected if the interval between acquiring the disease and marriage was over five years. They felt, however, that the five-year rule was surrounded by too many uncertainties to be considered absolute. Klingbeil and Clark (1941) found that there was no instance of conjugal infection of the marital partners of patients whose disease had been present four years or more before marriage, whether treated or untreated.

So far as we can determine there is no proper evaluation in the literature of the effect of treatment on the transmission of syphilis, although it is generally assumed that arsenical therapy rapidly reduces the possibility of infectiousness. O'Leary and Williams state that in a small group of 18 patients who received adequate treatment (twenty or more injections of arsphenamine and heavy metal) within the first year of infection and who had married before the disease was two years old 6 (33 per cent) of the partners were infected. The incidence of infection of the partner in this series was 40 per cent among those who had been inadequately treated for their early infection.

It should be remarked that most approaches to the problem of conjugal syphilis are clouded by the impossibility of evaluating the importance of extramarital exposure (after marriage). Often the true facts are shrouded in secrecy by the conventional attitude of the patient. Whereas many authors make the statement that they believe the answers to their queries are reliable, even a few misstatements or misinterpretations on the part of the patient could considerably distort the results in the relatively small series of cases that are usually the basis for such reports.

Both O'Leary and Williams and Klingbeil and Clark articles give suggestive evidence of exposure of the marital partner to infectious lesions without transmission of the disease. In the Mayo Clinic series, there were three families in which repeated sexual contacts occurred while one or the other marital partner had active lesions of the mucous membranes which contained *Spirochaeta pallida* and, though prophylactic measures had not been used, not one of the marital partners was infected.

The case histories of Chapter XIII will serve as reminders of prolongation of the infectious period by ineffective treatment or phenomenal resistance. It is evident, therefore, that neither unqualified pessimism nor a careless optimism is justified in estimating the risk of marital transmission in syphilis. Instances of the late transmission of the disease always bulk large on the clinical horizon and exaggerate the unfavorable impressions. But in spite of this fact it is perfectly apparent that unqualified assurance regarding the fitness of a syphilitic patient for marriage cannot be had.

Other Considerations in the Marriage of Persons with Syphilis.—Transmission of the disease to the marital partner while the most important is not the only issue in the weighing of fitness to marry. The acquiring of a syphilitic infection, especially by the male, induces automatically a certain inescapable risk of future breakdown. The families of such patients may become a cost to the community, to say nothing of the social loss entailed by the removal of parental influence. The younger the patient with syphilis who seeks marriage and the less prepared economically to meet the risk of complications, the more cautious should the physician be in sanctioning the establishment of a family.

Economic Consequences of Paternal Syphilis.—While the risk of late involvement of the central nervous system and cardiovascular system do not loom as large with ideal treatment as

they did in times past, yet, under average conditions of modern therapy they are still important considerations. The age period thirty-five to forty-five, as has been most apparent from the studies of the preceding chapters, is the one in which the most disabling consequences of syphilis make their appearance. The damage done to the integrity of the family in its critical years is most apparent. Industrial declines (see Stokes, Beerman and Ingraham, Syphilis and Industry 1938), personal and marital anxieties and discords, the incapacitating and disrupting influences of syphilis and the ultimate costs to the state of family wreckage which must be salvaged or sustained, take huge aggregate toll of the community and social resources each year (Beerman, 1940, Costs of Syphilis)

Dalton (1937) determined that the life of white males with syphilis between thirty and sixty years is shortened 17 per cent and that of Negro males 30 per cent as compared with the general population. Lilleywhite (1940) in analyzing the statistics from group of relief applicants in Fulton, Ga., found that illness resulting in time lost from work, was greater in syphilitics than in nonsyphilitics and that only 51.9 per cent of syphilitics could do hard labor as compared with 92.0 per cent nonsyphilitics. The predisposition of syphilitics engaged in heavy work to develop cardiovascular involvement has been shown by Cochems and Kemp (1937). Of one hundred syphilitic paretic men investigated by Williams, seventy-eight were married and left debit of $218,948 in lost earning power and the one hundred men cost the state $30,518 for their personal support until death. One hundred nine children were left to their own resources without the adequate protection of their parents. Solomon and Solomon found that 63 per cent of the families of 41 paretics required permanent financial aid. I 50 per cent the family was more or less completely disrupted.

Fitness for marriage varies, then, first with the duration of the disease in the infected party· second, with sex, women being almost more uncertainly eligible than men because of the possibility of transmission of the disease to the unborn child third, with the course of the individual infection. "Mucous relapses," neurosyphilitic patients, serological recidivists, and fixed positive cases must be judged solely on their individual merits. The amount of treatment given the infected person is the fourth criterion. It should meet the best proved requirements of the present day as outlined in previous chapters. In the fifth place the economic responsibilities to be assumed have a social right to consideration. The marriage of elderly noninfectious syphilitic patients in easy circumstances is a matter of small concern. That of young and recently infected partners with the prospect of children and an unknown economic future confronting them is an issue of great concern to themselves and to the state.

Theory vs. Practice in the Marriage of Syphilitic Patients.—Difficult though it is to outline theoretically sound requirements for fitness to marry it is vastly more difficult to induce acceptance of such theoretical requirements in practice. It is a very practical fact that the majority of patients will give little consideration to rules in their individual decision to marry While theoretical requirements like those of Fournier grow more rigid as the individual proponent s experience broadens, willingness to adhere to a decade of celibacy decreases with the youth of the patients. We are inclined to believe that the ultimate control of the marriage of syphilitics will come through a practical proposal for protected or precautionized marriage, unless infallible cure can attain the celerity of a one-week affair

Conservative European opinion has been summarized by the Hoffmann rule, which is little more stringent than that of Finger and calls for three years of treatment with arsphenamine and heavy metal, and two years of symptom-free observation before marriage. In terms of the second decade of the twentieth century instead of the first, this freedom from symptoms would include repeated negative blood and spinal fluid from the end of the first six months of treatment.

French opinion, summarized in the report of commission for the study of the question which included in its membership Queyrat, Hudelo, Spillmann, Gastou, and Simon, differ-

entiated between serologically positive and seronegative primary syphilis, permitting the latter to marry at the end of two years with only one year of treatment if he had remained free from secondary symptoms the first year while the seropositive case was expected to take treatment for two years. Even though the blood Wassermann reaction remained positive at the end of the second year marriage was permitted if the spinal fluid was normal. A positive spinal fluid examination at the end of the second year or other evidence of neurosyphilis was accepted as a definite bar to marriage, and positive accounts of both duration of infection and amount of treatment were to be required of all patients.

Our personal theoretical requirement for the marriage fitness of the average early case would approach the Hoffmann rule. Adequate treatment would be defined as presented in Chapter XIV carried through regardless of initial or interim negative blood Wassermann tests but seriously regardful of any tendency to positive serological relapse It is not as yet possible to define fitness to marry in terms of the newer rapid methods of therapy so that duration of the disease plus treatment must be considered a safer criterion than treatment alone. The spinal fluid must have been negative long enough to convince the experienced consultant that neurosyphilis has been completely overcome The cardiovascular examination must be negative at all points in the fifth year Such a rule somewhat less detailed in its provisions, had already been adopted by the All American Conference on Venereal Disease at Washington in 1920 as the accepted American practice.

Prevention of Infection in Marriage.—Measures to prevent the transmission of syphilis in marriage must be based upon the statements previously made regarding the infectiousness in some cases of even slight abrasions of the genital mucosae both male and female and upon the bringing about of pregnancy at times when the husband and wife can be assured so far as present knowledge permits, that neither is in an infectious condition. The precise instructions which the physician in whose hands the matter should always rest, may give to the individual pair to whom he gives permission to marry or whose marriage he must supervise within the infectious period of the disease, will be limited by his state and national laws, which in striking at contraception hamper the control of infectiousness in some instances. Only a mechanical protection in the form of an inspected and approved condom which absolutely precludes contact of infectious lesion or secretion, with uninfected surface is adequate in our present knowledge of the transmissibility of syphilis. There is as yet no effective gel or ointment to be used in intercourse. The value of chemical prophylaxis in the woman is virtually unknown. Special precaution should be observed during periods when the patient is not on spirillicidal treatment, with some relaxation permitted when he is and finally possible systemic prophylactic treatment may be given to the syphilitic mother during gestation even though she may be at the time serologically and clinically negative for syphilis. Under no circumstances should the mere negativity of the blood serologic reaction, especially in an early case be made a ground for withdrawing precautions. Measures for preventing transmission of the disease to marital partner and child must remain in force during a period of years, while the disease becomes spontaneously noninfectious, and could well be in some particulars, extended throughout the reproductive life of the parties. By such a series of measures pregnancy would be given some assurance of a healthy beginning and ending even within a year or two of the date of infection and the weak spots in a time-treatment system could be controlled to as full an extent as the peculiarities of the disease permit.

Extramarital escapades and dissemination of infection, an incidental consideration not to be overlooked, would thus also be reduced to a minimum. The testing out and adoption of such a system of marital control in syphilis must, of course, await public education to the necessity for it, the accessibility of the means for carrying it out, and experimental studies of the most effective aids.

In effect such a "precautionized" or "protected" marriage during the theoretical infectious period of syphilis supplants the always somewhat hazy concept of "safe" marriage which, in our experience is the hardest thing in the whole field of modern syphilology to define for the particular case. While it may well be asked how closely a married pair would follow a regimen of "precautions," our observation indicates a much closer adherence could be secured than to one of abstinence.

The Partner Must Know the Facts.—Any plan for the control of infectiousness in marriage, whether it begin with a five-year rule or none requires as a basic feature full information as to the situation given to the noninfected partner before or in marriage. It is unconscionable social and medical short-sightedness, to say nothing of unpardonable cruelty and dishonesty to sanction any withholding of the facts from the woman or man who is asked to take the risks inseparable from our only too patent ignorance and fallibility

It is interesting to note that of the numerous State premarital laws recently enacted, that of Virginia is unique in permitting medical certification for marriage of syphilitics only after: (1) *informing both parties of the fact*, (2) discussing the possible consequences of the infection, (3) reporting them to the state health department and (4) securing the infected person agreement to pursue treatment until dismissed. Failure to continue regular treatment then constitutes misdemeanor punishable by court action.

Legal Status of Marriage in Relation to Syphilis.—Scandinavian countries in particular have had laws requiring freedom from venereal disease in the contracting parties to marriage. In 1935, the first state law in this country requiring blood test for syphilis was adopted in Connecticut. By 1942, thirty states had laws requiring some type of examination for syphilis before marriage. Twenty-seven of these states required blood serologic tests, as follows

California	Kentucky	New York	Pennsylvania	Vermont
Colorado	Maine	North Carolina	Rhode Island	Virginia
Connecticut	Massachusetts	North Dakota	South Dakota	West Virginia
Illinois	Michigan	Ohio	Tennessee	Wisconsin
Indiana	New Hampshire	Oregon	Utah	Wyoming
Iowa	New Jersey			

As of April, 1943 (Mahoney) the District of Columbia and eighteen states, as follows, still had no legislation directed toward venereal disease control in marriage

Arizona	Florida	Maryland	Montana	Oklahoma
Arkansas	Georgia	Minnesota	Nebraska	South Carolina
Delaware	Idaho	Mississippi	Nevada	Washington
District of Columbia	Kansas	Missouri	New Mexico	

The differences between the various laws which have been enacted have been summarized by Forster and Shaughnessy (1942), Peckham (1941) and Edwards (1940). Many of the laws have been drafted without due regard to our knowledge of the transmission of syphilis but some conform t the ideal statute which has been suggested by Johnson (1938, 1939).

The Model Marriage Law with respect to syphilis embodies the following: (1) that both applicants for marriage license be examined for syphilis by licensed physician, (2) that the examination be both clinical and serologic including blood test of type approved by the state department of health, preferably in an approved laboratory (3) that the tests should not be made more than thirty days before the license is applied for and that the license when issued be

valid for not more than sixty days; (4) that the blood test when necessary be performed without charge on request through the health department; (5) that the filing of a certificate of medical examination may be waived by the judge of a proper court because of an emergency or some other cause. With this single exception, the physician must file a certificate of examination accompanied by the report of the laboratory test, which includes the name and address of the applicant, the date and type of test, but not the result. The result of the test should be filed with the medical record. (6) The decision as to the issuance of the medical certificate is left to the physician. He may certify the applicant even though syphilis is present, provided he feels that the applicant is in a stage of the disease which is not likely to become communicable. Otherwise treatment must be given and the immediate issuance of the certificate refused. The remaining portions of the model law deal with instructions to the licensing authority to persons performing the ceremony and provide a penal clause.

Prenatal Examination Law.—Up to the end of 1940 there were nineteen states in which physicians were required to examine pregnant women for syphilis:

California	Indiana	Maine	New York	Rhode Island
Colorado	Iowa	Massachusetts	North Carolina	South Dakota
Delaware	Kentucky	Michigan	Oklahoma	Washington
Illinois	Louisiana	New Jersey	Pennsylvania	

In general the prenatal examination law requires that a serologic test for syphilis be made at the time of the pregnant woman's first visit to her physician. The test must be a standard one done in an approved laboratory. On request the test may be made without charge by the health department. The birth certificate of the child should state whether the test has been made, and if it has not, the reasons for failure to make the test must be given. The results of the test itself should not be recorded.

The Value of Premarital and Prenatal Legislation.—There has been considerable difference of opinion among physicians as to the worth of and justification for such laws. This has been summarized by Stokes and Ingraham (1939), Moore (1939), Nelson (1939), Kolmer (1939). Most are in agreement that they have great educational value for the general public, as was pointed out by Hall as early as 1925, in connection with the Wisconsin law. Some feel that this type of legislation is a great social advance.

It will be many years before premarital and prenatal legislation can be evaluated. The more important benefits to date include: (1) *the discovery of a large number of hidden cases of syphilis.* Sheppe (1941) in analyzing the results of 677,832 premarital blood tests from 13 states found 9,017 (1.3 per cent) positive. Edwards (1940) states that between 70 per cent and 90 per cent of these individuals did not know they had syphilis, at the time the examination was made. (2) *The prevention of the spread of syphilis by preventing the marriage of infectious individuals.* Hall (1939) analyzed the disposition of 258 seropositive premarital cases in New Jersey and found that marriage certificates had been granted to 45 per cent and refused to 33 per cent (no report on 5 per cent). In the 147 instances in which the certificate was refused 61 per cent were not legally married and 20 per cent were married outside the state (in 19 per cent the outcome was not known). (3) *Decrease in the incidence of congenital syphilis.* Talbot (1940, 1942) venereal disease control officer of Connecticut, the first state to pass such legislation, found a marked decrease in the reported new cases of syphilis under one year of age in a four year period 1936—35 cases; 1937—24 cases, 1938—16 cases, 1939—11 cases. Since then, the rate has become about stationary; 17 cases were reported for 1941. Although reporting of syphilis, in most areas, is grossly incomplete, this may indicate a trend. Howard (1941) states that in Massachusetts the reported cases of congenital syphilis under one year remained stationary between 1930 and 1937, but after that they have shown a sharp drop until only 8 were reported for the entire state in 1940.

Medical Examination for Syphilis before Marriage.—In the face of widespread legislation directed toward the prevention of familial and prenatal syphilis most of which depends upon a blood serologic test it must be reemphasized that there is *no single infallible test of fitness* for either marriage or pregnancy. The negative blood test, too often relied upon by both the physician and the patient, may be wholly untrustworthy. The positive test, if it results from syphilis at all, will have no necessary bearing upon possible infectiousness. In spite of the legislative confidence that has been voted it, it has, when used alone, a limited deciding value in determining either the

presence of the disease or its transmissibility. A complete appraisal of the case is necessary.

Such an examination should include a carefully taken history, serological tests checked on separate samples of blood, sent, if possible, to two laboratories, and a complete physical examination for syphilis. If evidence of a previous or probable syphilitic infection presents, the examination should be carried farther, may include a period of observation, and may require interpretation by an expert. If reasonable doubt as to the validity of the serologic positive (biologic false positive) exists, expert appraisal of the case by a competent syphilologist should be made available by the state health authority. The basis of such a check is outlined in Fig. 87. There is no single landmark or milestone which when passed indicates fitness for marriage.

THE SYPHILITIC FAMILY

The Proportion of Infected Individuals in the Syphilitic Family.—The family in which a syphilitic member has been discovered will include between twenty and forty per cent syphilitic individuals depending upon the stage of the disease, the number of children in the family, and the effectiveness of antecedent therapy for syphilis. Numerous epidemiologic studies which have been performed in various sections of the country during the last ten years have shown that with early syphilis, the marital sex contact will be infected on an average three fourths of the time and that about one third of the immediate members of the syphilitic family will be found to be diseased.

The Solomons in a survey of 555 families largely with late syphilis, some years ago found 22 per cent syphilitic individuals. Casselman and Cadwallader (1939) found 35 per cent of their family syphilis contacts to be infected, all stages of the disease being included. When early syphilis is present this figure may approach 40 per cent.

Other members of the household who have not been exposed sexually to the original patient will have about the same prevalence rate of syphilis as would be expected from that class of individual in the community as a whole. The summary of Clark's (1940) work may be considered typical of the average clinic in which 62 per cent of the patients are Negro.

In discussing the high prevalence of syphilis in siblings over fourteen years of age living in the same household, E. G. Clark (1940) states that this probably indicates family promiscuity rather than transmission directly from one member of the immediate family to another. In our experience it is not infrequent for various members of the same household to acquire syphilis from different sources outside the family. A word of caution is sometimes necessary in interpreting such a situation lest these extra household infections be too readily considered as having occurred from exposure within the immediate family.

Prevalence of Syphilis in Children.—With the decreasing incidence of congenital syphilis which should follow the better medical care of the syphilitic woman at the time of marriage and during pregnancy, the generally accepted estimates of the prevalence of congenital syphilis at about 3 per cent (Vonderlehr 1936) in the population at large, will probably turn out to be too high. This figure even now applies largely to the public clinic class of patient and not to the population of the country as a whole where rates are apparently much lower, but much more difficult to determine because of failure to file public health morbidity reports.

Jeans (1921) noted the striking differences produced by social status. In St. Louis 16 per cent of colored infants, 1.8 per cent of poor whites and less than one per cent of infants in well-to-do families had the disease. The Cooperative Clinical Group studies, with Cole (1940) as spokesman, estimate that each year syphilis is transmitted to at least 85,000 fetuses in the country 25,000 of which die before birth and 60,000 of which are born alive with syphilis. They further express the opinion that about 10 per cent of fresh syphilis is congenital in origin. The high mortality of syphilitic conception in the untreated syphilitic mother and the effectiveness of antepartum therapy when the disease has been discovered, keep the proportion of infected children in the population lower than that in adults.

Syphilis in the Parents.—While the ease of demonstrating syphilis in the mother or father will vary with the age of the congenitally syphilitic child, and hence that of the parent, a careful appraisal of the family situation, including serologic testing, will usually though by no means invariably give valuable diagnostic leads. In the original Mayo Clinic Series 69 per cent of the mothers and 50 per cent of the fathers (90 men and 139 women) examined showed clinical or serological evidence of syphilis. Jeans and Cooke (1930) reported 85.8 per cent of mothers and 56.4 per cent of fathers seropositive. With preponderantly infant material the proportion will tend to be higher. Thus, in Wile and Mundt's (1942) series of 98 infants with congenital syphilis, there was no instance in which the family history was negative for syphilis (in 95 per cent the mothers had a positive blood serologic test and in the remaining cases there was hearsay evidence unsupported by laboratory findings). These same authors found that in 402 patients with late congenital syphilis the family history corroborated by serologic tests was positive in 74 per cent and that in an additional 20 per cent the history was doubtful. In only 6 per cent was history completely negative with negative blood tests in parents and siblings.

On the other hand, wholesale serologic testing of young adults (the selective service system, premarital examination, etc.) is disclosing persons with clinical stigmas of congenital infection and positive serologic tests, whose parents, now in their old age, may one or both be seronegative. The difficulty of conducting an adequate history-taking and examination of such parents is considerable and caution must be used in evaluating their status by blood tests alone, in relation to the now adult child's congenital infection.

Sterility in Syphilitic Families.—If sterility be defined as the inability of childless couples to conceive, there is no reason to think that syphilis, in itself, is an important cause of sterility in syphilitic families. Gonorrhea may be responsible for a portion of sterility in syphilitic families. Untreated syphilis may cause childless marriages through miscarriage or neonatal death of the diseased fetus, but seldom through involvement of the reproductive organs themselves.

Syphilis of the ovary in the acquired form of the disease is virtually unknown (Warthin, 1928) and syphilitic lesions elsewhere in the female genital tract have not been shown to impede fertilization. Hubner (1940) states that in the male a history of syphilis is a rarity in either impotence or sterility cases, though Ritter (1937) lists it among the infrequent causes of sterility. Treatment of the male syphilitic alone has been known to result in the birth of a healthy child (Moore, 1923), and Hagner (1925) reports a case of bilateral gumma of the testicle in which spermatogenesis was restored by treatment.

Syphilis is listed by Tew (1939) and Burns (1940) among the systemic diseases which may be associated with sterility through upsetting the normal constitutional balance. Hamilton (1941) reporting on the etiologic factors in 483 patients in the sterility clinic at Bellevue Hospital, N. Y. C., found syphilis to be a factor in only 2 per cent (in four cases it was felt to be the primary cause and in four a contributory factor). Béclère and François (1938) rated syphilis as never a primary cause of sterility in women, but felt that it was a secondary cause in 3 per cent of their cases.

Examination for syphilis should always be made in patients complaining of sterility and

appropriate treatment instituted if the disease is discovered. In most instances, however the sterility will be found to result from conditions other than syphilis.

Birth Rate of Syphilitic Families.—The live birth rate of untreated syphilitic mothers is only a little more than half as high as that of the general population. This arises largely from the fact that syphilis affects reproductivity largely through its damage to the fetus prior to birth. On the other hand, those syphilitic mothers who conceive may do so at a higher rate than the general population, which is probably explained by the short course of a large proportion of the lost syphilitic pregnancies. According to the Solomons, the syphilitic birth rate is 2.06 as compared with 3.8 in a similar social group. Harman found 150 syphilitic mothers responsible for 1001 pregnancies, while 150 healthy mothers had only 866 pregnancies. Jeans and Cooke found 4.8 pregnancies the average in 250 syphilitic families, 4.9 per cent in 250 nonsyphilitic families. A more recent series (1936–39) reported by Dill, Stander and Isenhour (1940) of 386 syphilitic and 414 nonsyphilitic women gives rates of 3.0 and 2.7 respectively. These figures will tend to become identical as prenatal therapy of the expectant mother may be universally applied.

Mortality and Morbidity of Syphilitic Conceptions and Living Children.—Untreated syphilis may be a major cause of loss of life of the fetus during the latter months of pregnancy and of the infant during the first few months of postnatal life. Although many of the studies which appear in the literature fail to take fully into account the normal fetal and infant mortality of a nonsyphilitic control group, the disastrous effects of untreated syphilis are unmistakable. The older literature on this subject has been completely reviewed in the previous editions of this text and by Ingraham and Kahler (1934). Without dwelling upon individual experiences, these studies collectively show that the incidence of stillbirths is roughly eight times more frequent in the untreated syphilitic mother than in the population at large and that, whereas the infant death rate during the first week of life is about three times that of the average for the country by the end of the first year of life about four in every ten will have perished. Fully one half and in some groups larger percentages, of the living children are moreover syphilitic.

Literature in the last decade gives a similar picture. McKelvey and Turner (1934) found of their untreated syphilitic mothers only 34.1 per cent had live births and of these 64.5 were syphilitic. McCord (1936) reporting on 3000 syphilitic deliveries, stated that the untreated mothers gave birth to dead or diseased children 65 per cent of the time. Halloran (1939) had two stillbirths and 11 diseased children in 16 untreated syphilitic pregnancies and Benesohn (1942) reported 61 per cent dead or diseased children in 146 untreated diseased mothers.

The general application of antepartum therapy to the syphilitic woman has made the majority of studies descriptive of fetal and infant mortality from syphilis a decade or more ago, inapplicable to the present situation. Even greater advances in this field are to be expected in the immediate future. Stillbirths and neonatal deaths from syphilis are already uncommon in centers where treatment is readily available and the standards of medical practice high.

Dill, Stander and Isenhour' (1940) well controlled study of two separate groups of syphilitic mothers may be considered typical. They found in their syphilitic groups 77.1 per cent and 91.6 per cent full term living children as compared to 96.9 per cent and 96.3 per cent respectively in their control group; dead born children were 7.3 per cent and 2.5 per cent in the syphilitic group compared with 3.0 per cent and 0.7 per cent for the control groups; and neonatal deaths 4.8 per cent and 2.7 per cent in the syphilitic group as compared with 0.5 per cent and 0.2 per cent in the control group.

In the obstetrical clinic at Western Reserve University stillbirths resulted four times as frequently among the syphilitic as among the nonsyphilitic women (Cole, 1936). As late as 1941, Peckham stated that 10 per cent of the last 1000 consecutive fetal deaths occurring at Johns Hopkins in the preceding ten years resulted from syphilis.

Jeans (1921) noted the striking differences produced by social status. In St. Louis 13 per cent of colored infants, 1.8 per cent of poor whites and less than one per cent of infants in well-to-do families had the disease. The Cooperative Clinical Group studies, with Cole (1936) as spokesman, estimate that each year syphilis is transmitted to at least 85,000 fetuses in the country 25,000 of which die before birth and 60,000 of which are born alive with syphilis. They further express the opinion that about 10 per cent of fresh syphilis is congenital in origin. The high mortality of syphilitic conception in the untreated syphilitic mother and the effectiveness of antepartum therapy when the disease has been discovered, keep the proportion of infected children in the population lower than that in adults.

Syphilis in the Parents.—While the ease of demonstrating syphilis in the mother or father will vary with the age of the congenitally syphilitic child, and hence that of the parent, a careful appraisal of the family situation, including serologic testing will usually though by no means invariably give valuable diagnostic leads. In the original Mayo Clinic Series 69 per cent of the mothers and 50 per cent of the fathers (99 men and 139 women) examined showed clinical or serological evidence of syphilis. Jeans and Cooke (1930) reported 85.8 per cent of mothers and 56.4 per cent of fathers seropositive. With preponderantly infant material the proportion will tend to be higher. Thus, in Wile and Mundt's (1942) series of 98 infants with congenital syphilis, there was no instance in which the family history was negative for syphilis (in 93 per cent the mothers had a positive blood serologic test and in the remaining cases there was hearsay evidence unsupported by laboratory findings). These same authors found that in 402 patients with late congenital syphilis the family history corroborated by serologic tests was positive in 74 per cent and that in an additional 20 per cent the history was doubtful. In only 6 per cent was history completely negative with negative blood tests in parents and siblings.

On the other hand, wholesale serologic testing of young adults (the selective service system, premarital examination, etc.) is disclosing persons with clinical stigmas of congenital infection and positive serologic tests, whose parents, now in their old age, may one or both be seronegative. The difficulty of conducting an adequate history-taking and examination of such parents is considerable and caution must be used in evaluating their status by blood tests alone in relation to the now adult child's congenital infection.

Sterility in Syphilitic Families.—*If sterility be defined as the inability of childless couples to conceive* there is no reason to think that syphilis, in itself, is an important cause of sterility in syphilitic families. Gonorrhea may be responsible for a portion of sterility in syphilitic families. Untreated syphilis may cause childless marriages through miscarriage or neonatal death of the diseased fetus, but seldom through involvement of the reproductive organs themselves.

Syphilis of the ovary in the acquired form of the disease is virtually unknown (Warthin, 1928) and syphilitic lesions elsewhere in the female genital tract have not been shown to impede fertilization. Hubner (1940) states that in the male a history of syphilis is a rarity in either impotence or sterility cases, though Ritter (1937) lists it among the infrequent causes of sterility. Treatment of the male syphilitic alone has been known to result in the birth of a healthy child (Moore, 1923), and Hagner (1923) report a case of bilateral gumma of the testicle in which spermatogenesis was restored by treatment.

Syphilis is listed by Tew (1939) and Burns (1940) among the systemic diseases which may be associated with sterility through upsetting the normal constitutional balance. Hamilton (1941) reporting on the etiologic factors in 453 patients in the sterility clinic at Bellevue Hospital, N. Y. C., found syphilis to be a factor in only 2 per cent (in four cases it was felt to be the primary cause and in four a contributory factor). Béclère and François (1938) rated syphilis as never primary cause of sterility in women, but felt that it was a secondary cause in 3 per cent of their cases.

Examination for syphilis should always be made in patients complaining of sterility and

pregnancy only (c) Gräfenberg (1909) who has carefully studied the bacteriology of fetal syphilis and whose work has been confirmed by many European investigators and generally accepted (Schneider 1921 Matzenauer 1926 Pick, 1928 Klaften and Priesel 1930 Casazza, 1934 Levaditi *et al.*, 1935) Hoffmann (1938) states that he has discovered no embryo which contained spirochetes prior to the sixteenth week of fetal life. Histologic changes in the embryo suggestive of syphilis have been described prior to the fourth month (*cf* Orsós (1939) who found such changes in a 6 mm. [one month] fetus) but *Spirochaeta pallida* has not been found, which must cast some doubt on the syphilitic nature of these lesions. (d) Syphilitic skeletal changes have not been shown to occur prior to the sixth lunar month (Fraenkel, 1911 Alexander 1912) which would indicate that infection of the fetus had occurred not earlier than the fourth lunar month (*cf* Ingraham, 1936)

The maternal portion of the placenta may be infected as a result of the occasional showers of *Spirochaeta pallida* which gain access to the blood stream of the mother as in any active syphilitic infection. The ease with which the placenta is infected by means of the blood stream has been shown in rabbit syphilis by Uhlenhuth and Mulzer Kolle and Evers. The fact that the fetus occasionally escapes infection, even when the syphilitic mother goes untreated, may be explained, not only by the time which is necessary for the organism to penetrate from the maternal to the fetal tissues after spirochetemia has occurred but also by the circumstances which govern the accessibility of the organism to the maternal blood stream. These include the stage of the disease the amount of previous treatment and (especially with older infections) other poorly understood factors. In general however in the absence of treatment, the more recent the mother s infection with syphilis, the longer more intense and more frequent the bouts of spirochetemia and therefore the greater the chance of infection of the fetus (Cole, Jeans *et al.*, 1940)

The manner of passage of *Spirochaeta pallida* from the maternal to the fetal circulation has been variously explained and is probably not always the same. Most usual, perhaps, is the formation of an infected embolus which gives rise to small infarct in the placental blood vessels, through the walls of which the spirochetes may grow much as they grew through the Berkefeld filters in Noguchi experiments with artificial culture media. That no histologically demonstrable lesion is necessary for this transfer to take place, however has been shown by Trinchese (1910) *who found that in small veins the individual spirochetes were able to pierce the vessel walls without causing visible injury* Larger numbers of spirochetes ruptured the vessel wall in order to enter the blood stream.

A third mode of transfer has been suggested by Reitschel (1927), who feels that, in the majority of cases, it is unlikely that the spirochetes can pierce the intima and adventitia of the blood vessels, but gain access to the fetus by their own locomotion through the perivascular lymph channels of the umbilical vessels.

The reason that the spirochetal invasion of the fetus does not take place earlier finds, theoretically ready physiological explanation, when it is remembered that it is only after three or four months of pregnancy have passed that the cylindrical Langhans cell layer commences to atrophy and that it is not until the sixth month that it can no longer be detected. From this time on, the spirochetal invasion is at its height, very important protective cell layer having been removed (Kristjansen, 1927; Hoffmann, 1930; Trinchese, 1910, who found spirochetes penetrating the Langhans cell layer in only one per cent of the cases). Rooth (1914, 1918, 1920) and Macgillan (1930, 1933) have, moreover performed work which suggests spirochetieidal action of certain of the placental ferments.

Death of the fetus, when it occurs, is said to result from failure of adequate blood supply through closure of the placental vessels (Browne, 1927; McCord, 1929).

It should be borne in mind that for syphilis to be present in the fetus spirochetes must have passed over the placental barrier and the mere detection of syphilitic lesions on the maternal side of the organ does not necessarily mean fetal syphilis. Almost any large series of cases will show a few instances in which the placenta was diagnosed as syphilitic, but the child remained symptom free and serologically negative.

We may, with reasonable assurance, therefore, conclude that infection of the ovum before rupture of the Graafian follicle does not occur. Equally improbable is infection of the ovum at the time of fertilization. In rare instances *Spirochaeta pallida* invading the uterine cavity from infectious material deposited in the vagina after conception may traverse the decidua reflexa. But, it has been shown beyond question that whether preconceptional or postconceptional syphilis is in point, diaplacental invasion, especially in the latter half of pregnancy, is the habitual route.

SPECIAL PROBLEMS IN TRANSMISSION OF PRENATAL SYPHILIS

Diaplacental Passage of Infection to Fetus before Appearance of Primary Lesion in the Mother.—As might be expected, syphilis acquired by the mother in late pregnancy is readily transmitted to the fetus. Bickers (1942) reports an instance in which the fetus was infected prior to the appearance of the initial lesion which became clinically evident in the mother three days after delivery. The almost uniform passage of *Spirochaeta pallida* from mother to child when the disease is acquired in late pregnancy, almost irrespective of antepartum therapy, has been emphasized by Ingraham (1938), Moore (1930), Howard (1941). The supposed repressing effect of pregnancy on the symptomatology of maternal syphilis, which may make diagnosis difficult even though the disease is active, will be discussed in the section on the syphilitic mother to follow.

Syphilis Transmitted to One of Twins.—The general experience is that, with single ovum twins, both will either acquire or escape infection. Wolk's (1941) recently reported case of syphilis in one of identical twins does not bear careful scrutiny, principally because adult life was reached before the observation was made and because of the difficulty of differentiating between congenital and acquired syphilis at that age (see also Penrose, 1937, McKendree, 1937). Although we, personally, have never had the opportunity to observe an instance in which one of twins escaped infection while the other was diseased, with double ovum pregnancies, there are a few well authenticated instances in the literature where such a situation has occurred. Wile and Welton (1933) and Smith and Spence (1941) have completely reviewed the literature in this field, the latter authors' critical analysis revealing five case reports in which the phenomenon is well established to which they add four of their own. These "four instances occurred in the course of 44 twin pregnancies in forty women with syphilis," which makes the authors feel that the probability is by no means remote.

The infection of one of twins has, in the past, been advanced as possible evidence of paternal germinal transmission in which one ovum was infected, the other not. It would seem, however, that the operation of chance alone, with the diaplacental mode of transfer, would form a satisfactory explanation as to why only one of double ovum twins is at times infected. Under any circumstances, the protection afforded by the membrane separating the maternal and fetal circulation is such that occasionally in any series of pregnancies, the fetus escapes infection even in the presence of active, untreated maternal syphilis. The same explanation could apply to the infection of one of twins, the protection afforded by the placental barrier being the determining factor.

Instances in the field of congenital syphilis, in which one of twins develops more severe clinical manifestations of the disease than the other, are well known (Dennie, 1941, Hadsell, 1941, Cassel, 1933, Thoenes, 1942).

Third Generation Syphilis.—This subject is of interest for two principal reasons: (*a*) in determining the duration of infectiousness of syphilis through the placenta, and (*b*) in arriving at an opinion on the question as to whether it is necessary to be unduly concerned with the marriage or treatment during pregnancy of an expectant mother with a *bona fide* congenital syphilis, especially when she may have had adequate treatment for her own protection

during infancy or childhood. The diagnostic problems of this topic are also indirectly related to such considerations as acquired syphilis in infancy and childhood reinfection (superinfection) of congenital syphilitics and with the whole field of *Syphilis Héréditaire Larvée* which are discussed elsewhere.

The recent literature of third generation syphilis has been completely reviewed by Beerman, Wammock and Magnuson (1942) Although the experience of any one group of individuals in this field is so limited as to make authoritative statement difficult, an appraisal of the field would seem to indicate that there are few (probably less than ten) well established instances of third generation syphilis in the recent literature, and that the occurrence of the phenomenon is so uncommon as to cause little concern in questions pertaining to marriage or pregnancy

The older authors, while the cases presented by them do not always bear careful analysis in the light of the advances which have been made in the diagnosis of both congenital and acquired syphilis, still have presented group of criteria which are as valid today as when originally published. The much quoted Fournier Finger criteria include (1) Acquired syphilis must be demonstrated in the grandmother and preferably also the grandfather (2) prenatal as distinguished from acquired syphilis must be demonstrated in the mother of the third generation case. Acquired syphilis must be excluded in her case and the father must be proved to be healthy (3) There must be incontestable evidence of prenatal syphilis in the third generation. (4) Manifestations must appear soon after birth in both the second and third generations.

Indirect Hereditary Influence.—This topic has two aspects: first, the question of paternal influence on the second generation without infection of the mother and, second, the influence of both parents on the third generation and beyond, without the necessity of transmitting *Spirochaeta pallida per se*. In general, it may be concluded that valid instances of the influence of syphilis on the health of the next generation without actual transmission of the causative organism from mother to child, are, to say the least, hard to establish. It is equally difficult completely to deny the plausibility of the reasoning behind some of the examples brought forth in support of these ideas. A number of interesting observations in this field, however are worth mentioning.

Widakowitch has shown that the spermatozoa of the syphilitic patient are definitely abnormal structurally It is therefore conceivable that through chromosome or functional abnormality an abnormal slant may conceivably be imparted to the development of the fetus in an unknown proportion of cases. The frequency of testicular syphilis and the occurrence of seemingly healthy pregnancies in the wife following treatment of the syphilitic husband have both been cited as arguments in favor of male responsibility for the abnormalities of syphilitic fetus. On such foundation, if it could once be determined for both male and female, could be laid the elaborate structure of the French pediatricians and syphilologists discussed under the title of Syphilis Héréditaire Larvée.

Stokes has had one family suggesting these possibilities under observation in which 3 children were normal, though the husband was syphilitic. The mother herself was, so far as clinical demonstration goes, entirely healthy With the appearance of the symptoms of paretic neurosyphilis and the accompanying general physical deterioration in the husband, 2 pregnancies resulting in abnormal children ensued. The first of these (Fig 787) was typical Mongolian, though this abnormality should not be regarded as intrinsically suggestive of the influence of syphilis; the second and youngest child presented stigmata suggestive of heredosyphilis and had strongly positive blood Wassermann reaction. Such investigation is obviously too incomplete for final evaluation, but in view of the complete negativity of the mother and the first 3 children in the family the influence of the deteriorating syphilitic father in producing germinal dystrophy *in the last 2 children is at least strongly suggested.*

The summary by Bietschel (1931) of the differences between the German and the French points of view is courteous and generous, if politely incredulous, presentation of the subject of Syphilis Héréditaire Larvée. The conception of occult syphilis has the ardent support of most French pediatricians, including especially Martelli, Picard, Marfan, Hutinel, Lemaire. According to this group, the incidence of syphilis in France, including generations beyond the second ranges from 19 per cent (Lemaire and David) to 40 per cent (Hutinel) of the population. Included in the conditions grouped under the possible influence of *syphilis héréditaire larvée* are the following: (*a*) failure to gain weight at the breast (*b*) the atrepsies (athrepsia); (*c*) endocrine disturbances *such as myxedema and hypophyseal dystrophies of all types*; (*d*) bone and joint conditions on the rachitic borderline; (*e*) nervous diseases, including Mongolian and other idiocies, meningitis, hydrocephalus, Sydenham chorea and 15 to 50 per cent of mental disturbances; (*f*) gastrointestinal disturbances such as habitual vomiting, melena, obstinate enterocolitis in infancy; (*g*) forms of jaundice, especially in childhood, and the so-called "benign jaundice of infancy";

(h) chronic bronchitis and asthma, (i) congenital heart anomalies; (j) skin diseases of certain kinds, including vitiligo, sclerema, scleroderma and tuberculids, even infantile eczema, (k) hematopoietic disease, including the anemias of childhood, and enlarged spleen with anemia; and (l) lymphatic abnormality including general adenopathy and status lymphaticus. Other occult signs include intracranial hemorrhage (Voron and Pigeaud, 1909), increase in the size of the skull (Kamal, 1929; Marfan, 1927) inequality in the length of the fingers (Mikulowski, 1933) and epicranial phlebosclerosis.

Milian (1937) and Arcangeli (1936) have rediscussed the subject of dystrophic (as opposed to microbic) hereditary syphilis and Hoffmann (1938) has resummarized the German viewpoint in the statement "it may be regarded as certainty that the germ cells are not injured by syphilis toxins and that germinative syphilis does not exist at all.

Syphilis in the Father—Study of this question at once indicates how serious a matter it is to give the prospective father of a family unguarded assurances as to his "cure. A disconcerting proportion of the fathers we investigated married in good faith often following medical permission and



Fig. 787 —The two children of paretic father described above. There are three normal older children.

in the belief that they were cured It is a matter of considerable difficulty however to secure complete investigations owing to the reluctance of an apparently healthy man to submit to a week of tests. Approximately 50 per cent of the fathers of syphilitic children will have positive blood Wassermann reactions and 20 per cent will present suspicious but not diagnostic evidence It is important to realize that especially where neurosyphilis has appeared in the children the father may because he has not been protected by pregnancy show evidence which the mother does not. In the investigation of doubtful heredosyphilis this detail is often of value. Partial information was obtained on the condition of 99 fathers in our series, of whom 50 per cent had positive blood serologic reactions 18 per cent, suspicious signs, and 32 per cent were frankly negative. Jeans and Cooke (1930) report 50 4 per cent of fathers seropositive as compared with 85.8 per cent of mothers.

The Syphilitic Mother—The fact that the syphilitic mother presents few symptoms of her disease was recognized in the early writings on congenital

syphilis and postulated in Colles' law (1837). During the pre-Wassermann era, the absence of clinical findings in the mother was taken to indicate that she frequently escaped infection completely and that the congenitally syphilitic infant was the result of paternal transmission of the disease to which the mother was rendered temporarily immune by the pregnant state. Routine serologic testing of pregnant women *close to the time of the birth of the child* has indicated that when the newborn infant is syphilitic, the mother has a positive blood serologic test or other evidence of the disease in almost every instance. A typical example of the exceptional case in which it is next to impossible to establish a diagnosis of syphilis in the mother of the diseased child is reported by Handley (1940) (see also Waugh 1937). All those concerned with large volumes of pregnancy or congenital syphilis material see such instances occasionally. We are in accord with the opinion of most authorities that, on



Fig. 783.—The only clinical sign presented by the mother of two heredosyphilitic children—slight swelling of the right sternoclavicular junction. She was examined because her older child had symptoms, and her blood serologic test was found to be positive.

the whole the apparently normal mother of a congenitally syphilitic child is herself syphilitic.

The older the child with congenital syphilis before the disease is discovered, the more difficulty may be experienced in establishing the diagnosis of syphilis in the mother. The failure to take this into account in many of the reported series, confirmed with variations in the expertness of the physicians responsible for the original diagnosis of syphilis, account for the marked differences in the reported ability to detect maternal syphilis. In the original Mayo Clinic series dealing largely with late congenital syphilis, the mothers yielded positive blood serologic tests in 60 per cent, but later studies such as those of Jeans and Cooke found in younger material than ours, 85 per cent, and Wile in earlier material from the standpoint of age of infection, 95 per cent positive bloods. Good histories were obtained in mothers 3 per cent *vs* fathers 15 per cent; late syphilids, mothers 7 per cent *vs* fathers 13 per cent; neurosyphilis, mothers 12 per cent *vs* fathers 20 per cent. At best in our own study we were obliged to rate 21 per cent of the mothers of syphilitic children as negative

to an ordinary clinical and serological examination. It might be expected from the foregoing that the value of clinical history and physical examination in the diagnosis of syphilis in the infected mother would be extremely low in most instances. While it is unsafe to rely wholly on this means of investigation without resorting to the blood serologic test in addition evidence suggesting the presence of the disease is to be found in a surprisingly large number of cases. Various authors (Browne, 1922 Moore, 1923 Boas, Gammeltoft and Siecke 1926 Dodds 1927 Halloran, 1930) have found signs, symptoms or

Fig 780

THE VALUE OF AN ACCURATE HISTORY AND A CAREFUL PHYSICAL EXAMINATION IN DETECTING SYPHILIS IN PREGNANT WOMEN

(From Ingraham, "The Diagnosis of Inf ntile Congenital Syphilis during the Period of Doubt (Am. J Syph. & Neurol. 19 547 (Oct.) 1935))

Type of evidence.	Reason for reference		Diagnostic points actually found on history and physical examination with syphilis in mind.	
	No. pts.	% of 199 cases referred.	No. pts.	% of 239 total syphilitic pregnancies studied.
1 Positive Wassermann Reaction	165	84 3	196	82 1
2. Type of evidence other than positive serology *Total*	71	35 7	191	79 9
3 History of syphilis, *Total*	64	32 2	160	67 0
( ) Primary lesion			26	10 9
(b) Secondary lesions			31	13 0
( ) Inguinal lymphadenopathy			11	5 0
(d) Gumma			1	0 4
( ) Congenital syphilis			2	0 8
(f) Lat miscarriages or neonatal deaths in previous pregnancies	1	0 5	84	35 1
(g) Previou treatment or previous positive serology	63	31 7	109	45 7
(h) Husband syphilitic			57	13 4
( ) Previous living children syphilitic			13	5 5
4 Physical examination, *Total*	7	3 5	46	23 6
( ) Primary lesion	2	1 0	2	0 8
(b) Secondary lesions	4	2 0	14	5 9
( ) Scars and pigmentary changes from previous lesions			5	2 1
(d) Stigmata of congenital syphilis			3	1 3
( ) Aortic disease			28	11 8
(f) Signs of C N S. syphilis	1	0 5	9	3 8

history of syphilis in 23 to 64 per cent of mothers. (Refer also to the previous section on Syphilis in the Parents.)

Ingraham (1935) in a careful study of 239 syphilitic pregnant women at the Philadelphia General Hospital found that when the syphilitic pregnant woman was questioned alone *carefully* and confidentially with the thought of syphilis uppermost in mind evidence of the disease other than positive serology could be obtained in 80 per cent of cases, a number almost equal to those who possessed positive blood serologic tests (see Fig 780) Points in

the history were missed in about one-half of the cases, but only one seventh of the suspicious points in physical examination had been earlier detected. The points in history which Ingraham *found to be of greatest value* were (1) treatment prior to pregnancy (46 per cent) and (2) occurrence of late miscarriage or neonatal death in earlier pregnancies (35 per cent) story of symptoms suggestive of syphilis (25 per cent) and syphilis in other members of the family (21 per cent) Diagnostic physical signs of syphilis were present in the mother in only 10 per cent, but suggestive evidence was present in an additional 13 per cent. This emphasizes the necessity for routine blood serologic testing of every pregnant woman as recognized in the prenatal blood test laws.

The relatively asymptomatic course which syphilis seems to run in many women who have borne children, early gave rise to the idea that pregnancy exerts a beneficial effect on maternal syphilis (Swediaur 1809; Bertin, 1810; Colles, 1837) Ingraham (1934) has reviewed the literature on this subject and the effect of pregnancy on maternal syphilis has been effectively demonstrated from the standpoint of clinical statistics by the Cooperative Clinical Group Studies (1934) with Cole as spokesman. In surveying the records of 958 syphilitic women they found that among those who receive adequate treatment for this disease clinical progression occurred in only 4 per cent who had been pregnant since their infection was acquired and in 7 per cent of those not pregnant since infection. With inadequate treatment these percentages became 11 and 18 respectively showing progression. Pregnancy is most effective in ameliorating the course of syphilis once latency is reached, but also exercises this influence to a lesser degree in early infections. After the disease has progressed to the symptomatic late stage pregnancy is, if any thing, injurious. Among the adequately treated women, those with early syphilis showed 7 per cent relapse if pregnancy occurred after infection as contrasted with 9 per cent if pregnancy did not occur after infection. For latent syphilis these figures are 6.7 per cent and 5.4 per cent respectively while for late syphilis they are reversed: 10 per cent of the women who became pregnant after diagnosis of late syphilis was made showing evidence of progression of the disease as compared with only 3 per cent of those not pregnant since late syphilis developed. The occurrence of pregnancy in association with early syphilis is especially effective in reducing the incidence of central nervous system involvement and mucocutaneous relapse in the mother

Prolonged absence of clinical signs, leading to mistaken permission to marry is well illustrated by Fig. 435 (p. 642) One of us (Stokes) has watched the mother of a syphilitic boy for five years through a period of complete serological and clinical negativity only to have her develop a typical late syphilid of the cheek. In the present state of our knowledge, it is a safe clinical rule to withhold a pronouncement as to the condition of the asymptomatic mother of a syphilitic child and to regard her as in all probability a quiescent case

Blood Serologic Reaction in the Syphilitic Mother—The proportion of positive serologic reactions obtained in the mothers of syphilitic children will vary with the age of the mother and the child who is under investigation. The young mothers of syphilitic infants produce the highest proportion of positives because of the activity and short duration of their infections. Figure 790 summarizes the relatively small number of cases in the literature These results would seem to indicate that when we are concerned with late congenital syphilis, from two thirds to three fourths of the mothers may be expected to show a positive blood serologic reaction, but with early congenital syphilis this probability will usually exceed 90 per cent.

Proportion of Syphilis in Pregnant Women in General.—No accurate information on this subject has been available until recently since the publication of results of routine serologic tests on large unselected groups of the population through the application of prenatal blood test examination laws.

that the probability that the child will have syphilis exceeds 70 per cent. Cole *et al.* (CCG 1934) found that in a group of treated and untreated syphilitic women with a negative blood serologic test during pregnancy 81 per cent were delivered of living, apparently nonsyphilitic children, as contrasted with 57 per cent in mothers with a positive blood test. Moreover almost twice as many children were born alive but subsequently died among mothers with a positive blood serologic test, as among those with a negative test

The significance of a positive test on the pregnant woman from the standpoint of antenatal treatment varies, of course, with the age of the patient and the age of the infection and is subject to interpretations not unlike those which attach to the positive blood serological test in syphilis in general and to the test when employed as a guide to infectiousness. Belding wisely points out that the older mothers late in the course of the infection may bear healthy children even with strongly and repeatedly positive serological tests. The Cooperative Clinical Group Studies (1934 1936) were able to collect 58 women who became pregnant after being considered "cured" on whom the data furnished did not give evidence of a single syphilitic child having been born among pregnancies which occurred up to fifteen years after the infection. Birnbaum (1927) had previously reported 34 normal pregnancies among 21 "cured syphilitic women. The decision in such cases must be individual, however and one always has the feeling, perhaps in the hypersensitivity induced by modern 'paper syphilis that he is subjecting mother and child to unjustifiable risk of transmission of the disease if he decides not to treat. At least it may be said that the younger the mother and the earlier the syphilitic infection, the more serious the positive blood serological test and the more urgently does it demand treatment along the lines subsequently discussed

Routine Blood Serological Tests on Pregnant Women.—The enactment by many states of prenatal blood test laws has brought to national recognition the necessity for performing routine blood serologic tests for syphilis on every pregnant woman at the time of her first prenatal visit. Such a procedure will continue to be imperative as long as syphilis maintains an appreciable prevalence in the general population.

The fact that routine blood test for syphilis are not, even now universally applied during pregnancy makes it necessary to point out some of the studies which have indicated the desirability of such practice even though they have been performed many years ago. In hospital clinics for example Belding (1925) has shown for Boston that in 6000 maternity patients who were examined routinely without especial attention to syphilis, definite clinical signs were obtained in only 0 54 per cent and suspicious signs in 1 7 per cent, a total of 2.2 per cent whereas the blood serologic test for syphilis in the same group was 8.8 per cent. In Philadelphia, in 1931, the prevalence of syphilis was about 5 per cent in 25 prenatal clinics making routine serologic studies and it was only 1 per cent in 11 comparable clinics employing the test merely as they felt it indicated

Moore who has long vigorously attacked the objections of the physician in private practice to this problem was able to collect from his own practice 40 disasters attributable directly to the failure of the physician or obstetrician to make the required blood serologic study

It is well to remark that a single blood serologic test taken at the time of the first prenatal visit while it is probably the most valuable single diagnostic procedure in the control of congenital syphilis, will not completely control its transmission Aside from detection of the disease in the seronegative

syphilitic mothers above cited, it should be remembered that syphilis may be, and moreover not unfrequently is, acquired at the time of conception or even in the later months of pregnancy Such women may or may not present symptoms, depending upon the duration of their infection and the development of the normal clinical course of their disease prior to delivery The fact that a woman has had a negative blood serologic reaction early in pregnancy should not exclude syphilis *from consideration should suspicious signs develop* at a later date To detect all of these cases, moreover every pregnant woman should have, in addition to the initial blood test at the time of the first prenatal visit, a repetition of this test at, or near term. (Ingraham, 1939 Stokes and Ingraham 1939 Cole Jeans *et al.*, 1940)

Most active obstetrical services, particularly those of a large general hospital, or those which care for many unmarried mothers or sexually promiscuous women will have several instances yearly in which women, symptom-free and serologically negative early in the pregnancy develop clinical

Fig. 791.

THE MOTHER WHO ACQUIRES SYPHILIS AND BECOMES SERO-POSITIVE DURING THE PREGNANCY

B. D twenty-seven-year-old white woman, came under medical observation in the sixth month of her first pregnancy Complete physical examination, performed by the obstetrician, revealed no evidence of syphilis and a blood serologic test taken on the first prenatal visit was reported Kahn negative, Kolmer Wassermann negative Six weeks before *delivery this patient became ill at home with sore throat and slight temperature elevation* to 99.5 F; she developed number of discrete dusky-red papular lesions over her face and upper chest and some two to three eeks later several small papular genital lesions.

Prior to the development of this eruption she had contracted an acute upper respiratory infection and had been taking, internally salicylates, barbiturates and phenolphthalein. Reference as made to the previous blood serologic test which was found to be negative A second blood study was considered unnecessary The symptomatology presented was considered t be erythema multiforme from bacterial infection or dermatitis medicamentosa from ingested drugs. The fact that the mother in actuality had secondary syphilis as not disclosed until she gave birth t her infant. The infant manifested symptoms of congenital syphilis within forty-eight hours after birth and its infection as immediately diagnosed and treatment was begun. Both mother and child have had satisfactory clinical response.

syphilis or become seropositive before term. In some instances the disease has been acquired at the time of conception, the ameliorating effect of pregnancy on maternal syphilis frequently causing a prolonged incubation period and often a relatively symptomless infection. In other cases the disease is acquired through sexual relations in the early months of pregnancy to become clinically manifest close to the time of delivery and, rarely in the first week or two postnatally (See Fig 791 from Stokes and Ingraham Med Clin. N A. Nov., 1939)

Spinal Fluid Findings and Examinations in Syphilitic Mothers.—The repressing and protective effect of pregnancy in women with syphilis so far as the nervous system is concerned has been discussed. Wile and Shaw dealing with a youthful material, found 70 7 per cent to have normal spinal fluids, and 9 4 per cent to have abnormal spinal fluids, while 4 7 per cent showed an increase in cells or globulin alone After th sixth month lumbar puncture has a definite abortifacient effect which must be avoided. If the mother have *an early syphilis, the test may be done immediately postpartum for the detection* of meningeal involvement that may lead to neurorecurrence when the

demonstrated *Spirochaeta pallida* in 105 cases less than one third of which cases gave any degree of positive reaction on the mother's blood.

Macerated Fetus.—Maceration of the stillborn child was formerly regarded as almost diagnostic of syphilis. While it is undoubtedly suggestive, it is not pathognomonic and may be the result of other intoxications which result in the death of the fetus before birth The skull is collapsed, the abdomen protuberant, and the skin of the fetus appears as if scalded the epidermis being raised in enormous bullae containing a serous or hemorrhagic fluid and the underlying cutis being of a livid red color On handling, even the seemingly normal skin rubs off

About 45 per cent of dead syphilitic fetuses are macerated prior to delivery (McCord 1922, Holland and Lane-Claypon 1922, Cruickshank 1924) while between 64 per cent (Browne) and 80 per cent (Williams, 1918 Tecoul, Lasseur and Vernetlin, 1923, Morosoff and Raddin, 1928, Palmer 1928) of macerated fetuses are syphilitic. As syphilis becomes a less important cause of fetal death this latter percentage will obviously decrease.

Spirochaeta Pallida in the Fetus.—The finding of *Spirochaeta pallida* in the organs of the syphilitic fetus is being more frequently used as a diagnostic procedure as technic improves.

Browne obtained the organism by both darkfield and Levaditi impregnation in 8 of his 14 macerated syphilitic fetuses but found the organisms very much more difficult to find in the fresh than in the macerated specimens (1 in 21 as against 8 in 14). The difference may be due as Shaffer has found, to the reproduction of the organism in tissues under incubator conditions after death, and may justify the preservation of organs from such fetuses for later examination in the hope of reaching a positive diagnosis.

The Syphilitic Fetus—Pathologic Changes.—Histologic changes due to syphilis can be found in about 84.7 per cent of fetal autopsies (McCord) They are by no means invariably present, singly or together even in cases in which *Spirochaeta pallida* may be demonstrated (Fraser) so that a complete search may only reveal one or two distinctive features *Spirochaeta pallida* can be demonstrated in the tissues in about 35 per cent of the fetuses (McCord). Enlargement of the fetal spleen (30 to 60 per cent) and sometimes of the liver the presence of chondro-epiphysitis and fibrotic inflammatory changes in the lungs, liver spleen, and pancreas with tendency to multiple hemorrhage into the internal structures (Cruickshank) are the most distinctive gross pathologic changes as summarized by Fraser

Chondro-epiphysitis was regarded as very frequent by the older writers. Fabre and Bhenter found it in 74 per cent postmortem. Shipley *et al.* found by examination of 100 fetuses (sixth month to nearly term) with roentgen ray that 25 per cent showed marked syphilitic bone changes (osteochondritis) and 46 per cent had suspicious lesions. On the other hand, Olsen found it roentgenographically only once in 83 very young viable children of syphilitic patients and it was found in only one of Browne's 22 cases. More recently McCord has found an osteochondritis in 81 per cent of 243 syphilitic fetuses at autopsy The characteristic syphilitic alteration consists in the transformation of the epiphyseal line of the long bones into a thickened, irregular opaque yellowish-white band, sometimes resulting in separation of the cartilage and bone in the region Microscopically along the line of ossification of the bone there is seen proliferating connective tissue in which are areas of necrosis

The liver is not necessarily enlarged, nor need it show gross changes. The most constant alteration in the liver is general retardation in development of the organ, so that at birth there still persists the appearance of an active blood-forming organ (Jeans and Cooke). If enlarged it may simply be edematous and spirochetes be discovered in numbers in the stroma. Microscopically the column of liver cells form multinucleated masses the capillaries are distended and in places contain myelocytes, eosinophils, lymphocytes, and normoblasts. The rarer but quite characteristic pericellular cirrhosis produces an enlarged, hard, rounded liver with feel as of cutting rubber on section The color may vary from dark red to bile-stained green (flint liver) and the cut surface is speckled with opaque yellowish-white spots which are miliary gummas. Confusion with miliary tuberculosis is possible. Fraser emphasizes the absence of giant cell and epithelioid cells as in favor of syphilis Large hepatic gummas are rare.

The only constant change in the spleen is an increase in size, due to hyperplasia of the normal cellular elements. Microscopical examination reveals no histologic changes and usually only small numbers of spirochetes are present.

The changes in the kidneys may be fibrotic or consist of perivascular round-cell infiltration. Often combination of the two is noted in addition to an imperfect development of the glomeruli and, at times, areas of atrophy In rare instances rather diffuse acute interstitial nephritis is present (Jeans and Cooke)

Pancreatic fibrosis, which is common, resembles the inter- and intralobular fibrosis of the liver which causes wide separation of the lobules and acini producing slightly enlarged whitish somewhat gritty pancreas. There is also a developmental retardation with poorly differentiated acini and islands of Langerhans (Jeans and Cooke) The most common and most characteristic syphilitic lesion of the intestine (according to D'Aunoy and Pearson, 1930) usually confined to the small intestine, is raised, yellow plaquelike band which encircles the bowel. Generalized peritonitis may follow ulceration and perforation of these areas but may also occur in the absence of frank rupture. The lesions include necrosis of the mucosa and submucosa of the involved areas, miliary syphiloma and abscess-like foci. *Spirochaeta pallida has been seen in all layers of* the bowel and is especially prominent in the perivascular tissues and in the vessel wall.

The characteristic pulmonary lesion is fibrosis which results in an increase in size and weight of the organ. The fibrosis is usually irregular, producing pale, firm elastic patches of "pneumonia alba. The change is chiefly in the interstitial tissue. Microscopically the consolidated *areas reveal great thickening of* the alveolar walls by loose *edematous* connective tissue containing mononuclear cells and leukocytes. Desquamation of the alveolar epithelium may be seen in many places. The air cells are cubical instead of the usual flattened form and the smaller bronchi contain leukocytes and granular débris. Spirochetes are present in large numbers, more numerous in the consolidated lung tissue. In pronounced cases the lung may be heavy and airless although in the mild degrees of pneumonia alba there may be no detectable gross pathologic changes. Numerous authors, from Ricord (1845), to Virchow (1906) to Mraček (1893), to Warthin (1911) and many others since that date, have described involvement of the heart in autopsy examination of stillborn fetuses, or infants within the first few months of life. The characteristic lesions are of two types, interstitial myocarditis and nodular myocarditis, both occurring with about equal frequency *Spirochaeta pallida* has been demonstrated in these lesions by five authors in 1906 and by many investigators since then. The nodular lesion is not gumma, but localized syphilitic cellulitis or myositis (Williams, 1930) myxomatous in character (Warthin). Fatty degeneration of the heart muscle, though frequently seen, is probably better explained as the result of nutritional disturbances associated with the syphilitic infection, rather than as specific lesion. (*cf* Hinrichsen review 1943.) There is no apparent relationship between syphilis and congenital malformations of the heart.

The suprarenal shows definite changes in about 10 per cent of syphilitic fetuses (Fite) In addition to the large number of spirochetes the most frequent and characteristic change is an extraordinary amount of cellular connective tissue in the capsule, often projecting downward into the cortex, separating the groups of cortical cells (*perihypernephritis syphilitica*). Gummata *of the adrenal although* reported are rare.

Involvement of the testes is frequent but not so common as of the bone and liver. The testis may be laden with spirochetes even when no histologic changes can be recognized (Warthin) Macroscopical changes may be few although the testes may be enlarged in the early stages. The microscopical picture early is an inflammatory perivascular round-cell infiltration with subsequent interstitial fibrosis and destruction of the parenchyma, eventually resulting in trophy as summarized by Menninger The ovary although frequently containing large numbers of spirochetes, shows no constant pathologic change.

The thymus may be the site of multiple granulomatous changes and contain large numbers of spirochetes. The thyroid shows no constant pathologic lesion in the fetus, although it may contain numerous spirochetes.

Diagnosis of Syphilis in the Dead Fetus.—This must, as in other aspects of the disease, rest upon a combination of evidence, of which at times no one element may be absolutely pathognomonic. The investigation may be of great assistance in establishing the status of an asymptomatic mother Maternal and paternal study from all angles with elimination of any other assignable cause for the loss of the child and a careful search of the fetal viscera for *Spirochaeta pallida* are the less frequently used but important modes of

approach Rabbit inoculation of lymph node emulsion was positive in Manteufel and Herzberg's case The investigation of the family the maternal and fetal (cord blood) serologic test obtained by the accoucheur examination of the placenta and cord (the latter for *Spirochaeta pallida* both in section and darkfield) by a pathologist and pathologic and bacteriological autopsy study of the fetus should all be sought in the doubtful or suspected case. Roentgenological findings of Shipley and others and the observations of McLean (Chapter XVI) should be utilized. The clinical appearances aside from maceration which may reinforce the impression of syphilis in the stillborn child will be discussed in connection with early heredosyphilis.

THE LIVING SYPHILITIC INFANT

Types of Infection.—The fact that there are several ways in which the syphilitic infant or child may acquire his disease, and that the relative importance of these various modes of inoculation has been determined only in recent years, has led to much confusion in terminology in particular in the older medical literature By common usage the term *congenital syphilis*, though perhaps not the ideal designation, has come to include all forms of syphilis acquired prior to passage through the birth canal. The term *prenatal syphilis* introduced by Kolmer is preferred in this text for this type of the disease *Heredosyphilis* implies germinal transmission and has its origin in the older French literature, where these concepts abound. Hoffmann's (1936) classification from the older literature of infantile infection into *syphilis innata, connatalis postnatalis syphilis acquisita infantum* and *syphilis binerva* (Tarnowsky 1901) where both prenatal and acquired infection occur in the same individual, while scientifically exact has never gained wide acceptance in this country

Of more importance to the student than the question of exact terminology is a complete knowledge of the manner in which the infant may be infected. Most usual as previously described, is the diaplacental passage from mother to child *in utero* The acquired forms of the disease transmitted through (1) contact with infectious lesions or secretions in the mother's birth canal at the time of delivery (2) infection of the infant (or child) from exposure to infection after birth (3) acquired infection superimposed upon an infection occurring before birth while all are possible are extremely uncommon in actual practice

True prenatal infection involves an overwhelming of the child with organisms whose thoroughness often surpasses anything seen in the acquired form of the disease The child who survives such an infection does so by virtue either of special resistance or special protection. The mechanism of this protection is not established It may be that fetal tissues have an exceptional tolerance of the organism the chief evidence of it being the abundance of organisms in nonreacting tissues (heart, liver) The high fetal mortality of the disease speaks against special resistance as does its invasion of the nervous system in ways and degrees comparable to the adult acquired forms. It is very possible that the defence mechanism of the mother reinforced as it is known to be by her pregnancy is extended over the child *in utero*, and protects it as it does her It may be that the child's internal defence is in some way specially stimulated Clinically at least the child which survives an early uterine infection has a high resistance and makes a phenomenal response to intelligent treatment Extraordinary variability in the course of the infection

after birth may be attributed in part to the influence of the date of uterine infection, and in part, as in the mother to the suppressing and retarding effect of the special defence mechanism. Thus the child infected early in uterine life, or poorly protected presents at birth the changes of late syphilis, already far advanced. The child infected late in uterine life or who carries a suppressed infection through to birth at term, appears well during the first two or more weeks of fetal life and then develops lesions of secondary type, arguing a wide dissemination of the organisms. Most often a combination of the two processes occurs, and the child after birth develops, coincidentally with late lesions due to the long-suppressed infection early lesions of an infectious relapsing type Lastly the child infected early in uterine life with a relatively mild type of the disease may remain asymptomatic except for developmental stigmas for months or even years before showing active signs of the disease. This constitutes the tardive form of heredosyphilis.

Acquired Forms of Syphilis in Infancy and Childhood.—Syphilis acquired at the time of birth seems to be a comparative rarity possibly because the birth chancre is not recognized by the practitioner The development of lesions of a distinctly secondary type in an interval of six weeks to two months after birth, particularly if the mother be known to have had infectious lesions, should always lead to a search for the chancre on the infant. The chancre may occur upon the stump of the umbilical cord and some suspicion should attach to cases in which there is a prolonged delay in cord healing, with the formation of a distinct ulcer

Bumm reports as typical case the development of chancre on the cheek of child whose mother had four-week old chancre on the posterior part of the left labium minus t the time the child was born. This is congenital syphilis in the strictest sense, and is undoubtedly comparative rarity It seems probable, however that very lat hematogenous infection of the fetus, in the last tw months of fetal life, may give rise to the early eruptive picture and the general symptomatic sequence of an acquired syphilis.

Syphilis acquired late in pregnancy or at the time of birth is more difficult to recognize, lacking the "stigmas" of the uterine type and in many instances is not distinguishable from infections of extragenital origin, but obscure history contracted during childhood.

The unrecognized extragenital infection in infancy or childhood just mentioned should, in particular not be lost sight of especially in the inter pretation of juvenile neurosyphilis without the stigmas of the inherited type. While the actual extent of such infections cannot be estimated, enough case histories have been reported by individual observers as early as Fournier to justify a persistent campaign of public education against kissing and handling of infants by strangers and even relatives. The nurse-maid of uncertain credentials and the low-grade servant are the source of too many such tragic situations.

Several papers on the subject of syphilis acquired during infancy and childhood have appeared in the recent literature which tend to show that, while uncommon, it is by no means rare occurrence. Johns Hopkins Hospital, for example, had 45 cases under eleven years in the 17-year-period from 1921 to 1937 while 90 cases between eleven and fifteen years and 4,487 cases in adults occurred during the same interval. Waugh (1936) reports 21 cases eleven years of age or under; Smith (1930) 125 cases ten years of age and under (3 of these were less than one year 23 less than two years and 34 less than four years); Dyar and Goodwin (1941) 19 cases under fourteen years (8 cases under ten years). Shech and Long (1930) and Waugh (op. cit.) report four children and five children, respectively in single family with acquired infections,

which points out the pitfall of too hasty appraisal of such family situation, here the source of the children's infection could be attributed to a seronegative asymptomatic mother after the initial symptoms had cleared in the children. Smith's analysis showed the commonest method of infection in children to be attempted intercourse not infrequently with an adult (43 cases); after this came kissing, 16 cases, household contact, 14 cases, transfusion, 9 cases, unknown, 41 cases.

Superinfection and lesions due to birth trauma but containing organisms and even suggesting chancres, may be elements in the confusion borderline of "congenital and acquired syphilis," according to Hochsinger. Reinfection of patients with congenital syphilis is also known to occur, for discussion of which see the recent case reports and review of the literature by Hahn (1941) and Allison (1942).

Importance of Complete Evaluation of Maternal Syphilis Status.—The first and most important step in the medical care of the living syphilitic infant is to establish the presence of the infection in the mother. Just as the pregnant syphilitic woman is usually relatively symptom-free (see section on syphilitic mother), so the syphilitic infant is often asymptomatic at the time of birth and for the ensuing few weeks. Such clinical observations on the "healthy" syphilitic infant were formulated as early as 1865 into *Profeta's law*. While freedom from symptoms in the offspring of syphilitic parentage was a sufficiently frequent occurrence to be noted even in the prearsphenamine and pre-Wassermann era, with the partially treated syphilitic mother as in the usual situation today, it has become the rule. In clinic and hospital practice as high as 90 per cent of syphilitic infants may show no detectible symptoms of their infection during the immediate neonatal period.

Considering the detailed and expensive study over a period of many months, necessary for a proper medical appraisal of an infant to determine its syphilis status, it becomes physically impossible and financially impractical to carry out these procedures routinely under ordinary circumstances, unless examination of the mother raises a suspicion that she has syphilis. The syphilis appraisal at birth or during the first few weeks of life commences, not with a cord or neonatal blood test and a physical examination of the infant, but with a careful maternal history and a report of the mother's blood serologic test for syphilis during pregnancy. If it is found that the mother had no blood test for syphilis during pregnancy, then, in determining the likelihood of the infant's infection immediately after birth, it is just as important, and usually more enlightening, to obtain a specimen of blood from the mother as it is to test the child.

The Blood Serologic Test of the Newborn Infant.—At the time of birth and in early infancy, the blood serologic test for syphilis must be subjected to special study and interpretation. Even then it has a very limited diagnostic value in the first few weeks of life. It may be positive even though the infant is not diseased. It may be negative even though syphilis is present, at times, though rarely with active clinical manifestations. A seronegative syphilitic mother may give birth to a seronegative or rarely to a seropositive syphilitic child. Figure 792 gives the possible combinations of maternal and fetal serology and the syphilis status of the infant, along with some idea of the relative frequency of each type in clinic practice at the Philadelphia General Hospital. These percentages will vary somewhat from clinic to clinic, depending upon the activity of the maternal syphilis and the effectiveness of antepartum specific therapy in the cases used for analysis, but it becomes at once apparent that certain combinations are common occurrences while others are rarely encountered. Thus, it is very unusual to find a seropositive infant at birth if the mother is seronegative. The percentage of infants of seronegative syphilitic

mothers who will eventually develop syphilis and become seropositive at varying periods postnatally likewise is small.

Seropositive nonsyphilitic infants formed 8 per cent of the total group, but 13 per cent of the nonsyphilitic group and comprised *40 per cent* of the total positives obtained (see Fig. 794) This last mentioned percentage will increase with the adequacy of prenatal care and the corresponding decrease in the number of syphilitic infants born. Between 1938 and 1940 of 27 infants with positive blood serologic reactions at birth, 20 (74 per cent) did not have syphilis. There can be no question, therefore that **a significant number of infants, seropositive at birth, do not have syphilis,** and that the medical care of this type of case requires careful consideration.

Syphilitic infants, seronegative at birth formed about one fifth of the total series, but 28 per cent of the seronegative infants born of syphilitic mothers ultimately proved to have syphilis. Moreover only 30 per cent of the syphilitic

Fig. 794.

VALUE OF THE CORD AND NEONATAL BLOOD SEROLOGIC TEST IN THE DIAGNOSIS OF INFANTILE SYPHILIS

Various combinations of blood serologic reactions found in the syphilitic mother and her newborn child, as compared with the ultimate status of the child. (Philadelphia General Hospital series modified from Ingraham, Am. J Syph. and Neurol. 19 347 (Oct.) 1935 and Ingraham, Shaffer Spence and Gordon, Arch. Derm. and Syph. 43 365, Feb., 1941)

Type.	Serology of syphilitic mother	Infant serology at birth.	Ultimate syphilis status of child.	Number of cases.	Percentage total.
1	+	+	+	36	12
2	+	−	+	54	18
3	−	−	+	13	4
4	−	+	+	1	0 3
5	+	+	−	25	8
6	+	−	−	101	33 7
7	−	−	−	72	24
				302	100 0

infants were seropositive at the time of delivery This indicates that active medical follow-up of every child born of syphilitic parents is indicated, irrespective of its serologic status at the time of birth While it is true that a syphilitic child is considerably (perhaps three times) more likely to have a positive blood test at birth than a nonsyphilitic child and, while it is likewise tru that the majority (perhaps three fourths) of the infants seronegative at birth will not have syphilis, yet the probable occurrence of seropositive non syphilitic infants and of seronegative syphilitic infants is so great as to make the serologic test at birth unreliable as a basis for diagnosis or an indication for treatment of the newborn child

The Cord Blood Serologic Test.—Considerable discussion has arisen in the past over the desirability of depending upon the examination of blood from the umbilical cord. For detailed discussion of this see previous editions of this text and Ingraham and Kahler (1931) The chief objection to the use of umbilical cord blood is on the score of inadequacy rather than inaccuracy

The cord serum reagin content will usually compare closely with that of the venous blood of the newborn infant, but a single blood serologic test, cord or otherwise, can never be accepted as final elimination or confirmation of infantile syphilis.

It should also be pointed out that a cord blood serologic test cannot be considered a substitute for a test performed on the mother's blood during pregnancy or at the time of delivery for it will frequently be negative in the presence of syphilis in both mother and child. In the Philadelphia General Hospital experience the maternal blood serologic test in syphilitic women was positive at the time of birth in 71 per cent of cases (87 per cent in those who bore syphilitic infants) whereas the cord blood was positive in only 21 per cent. Less than one fourth of the syphilitic women could have been detected by relying on the cord blood alone.

The Quantitative Titered Blood Serologic Test.—The reason for the peculiar behavior of the blood serologic test in the offspring of syphilitic mothers is not clearly understood, but it is usually explained that there may be, in some instances, transfer of syphilis reagin from the

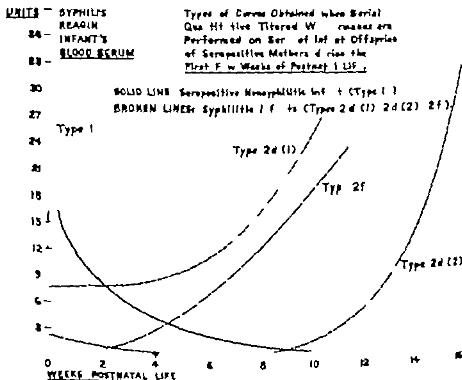


Fig 793.

maternal to the fetal circulation, irrespective of the transmission of *Spirochaeta pallida*. Antepartum treatment apparently is not a determining factor as was shown by Ingraham (1935).

The use of quantitative titered blood serologic tests (Faber and Black, 1936, Christie 1938, Davies, 1937 1938) has made it possible to show that, if the infant is not syphilitic the concentration of syphilis reagin in its blood stream is never more and usually considerably less, than that of the maternal blood stream. *The syphilis reagin will gradually disappear from the normal infant blood stream after some days or weeks* If the maternal blood serum reagin content, and hence the infant's, has been high, the infant titer will decrease rapidly at first, but after it falls to one or two units may persist at this level for many days (*cf* Fig. 793, Type 1).

If the infant, on the other hand, has syphilis, in rare instances, presumably when infection has occurred early in pregnancy and the infection is well advanced at the time of birth, the infant's blood serologic test may have a significantly greater titer of reagin than that shown by the maternal blood. This is considered to be of diagnostic significance. More commonly however, presumably when the fetus is infected closer to term, the infant titer will be in the same magnitude as the maternal serum reagin content for some days or weeks postnatally and may again

rarely decrease even to the vanishing point, only to increase again, rapidly and steadily as the disease becomes clinically manifest (Fig. 723 Type 2d (2)).

Ingraham, Shaffer Spence and Gordon (1941) experience has shown that more than one half of the seropositive nonsyphilitic infants had negative serologic reactions by the age of one month, but about 8 per cent persisted int the second month of postnatal life. Occasional cases have been observed in which complete seronegativity is not reached until from seventy to ninety days. In the sole instance in which the reagin titer of the infant serum was significantly greater than that of the mother' t birth, the mother' serum contained 8 units and the infant 64 units.

The quantitative titered blood serologic test has considerably greater value in eliminating the nonsyphilitic patient with positive serologic reactions, by detecting rapidly falling titer than it has in establishing an absolute diagnosis in the study of the truly syphilitic patient. Our experience has been somewhat in accord with Christie (1933), in that syphilitic infants with positive serologic reactions at birth seldom seem to show rapid or significant increase in the titer short of an observation period of one month to six weeks (Fig. 723, Type 2d (1)).

Our observation, further does not completely corroborate Black' (1930) statement to the effect that delay in diagnosis of from six weeks to two months is not harmful to the infant in some cases. Two babies in the 1936 to 1940 group, each with reagin titer fluctuating between 8 and 16 units on weekly determinations died at the age of sixteen and twenty-five days respectively while awaiting adequate serologic diagnosis. Both of these infants, though presenting no diagnostic lesions of the skin or mucous membranes, had both roentgenologic and autopsy evidence of syphilis.

While one is waiting four to eight weeks postnatally to determine the significance of positive test by serial titrations, repeated roentgenographic interpretation of the long bones will often suffice to corroborate diagnosis of congenital syphilis.

The Seemingly Healthy Child of a Syphilitic Mother —The observations of the majority of writers have indicated that the seronegative syphilitic infant will usually become seropositive by the age of two months, though we have seen very occasional cases, as have Roberts (1933) Dennie (1933) and McKelvey and Turner (1934) in which syphilis reagin was not detectible until the third or fourth month of postnatal life. Adequately studied cases of congenital syphilis in which the blood serologic test has not become positive by the sixth month are apparently so rare as to be of no clinical significance. While conservative opinion indicates a minimal two year and an ideal lifelong period of observation for the offspring of syphilitic parents, there is every indication that such prolonged follow-up is of value principally for purposes of scientific clinical research.

The fact that such a large percentage of infants, seropositive at birth, prove on prolonged observation not to have syphilis, makes most authorities at present feel that the apparently healthy child of syphilitic parentage should not be diagnosed as having the disease and should not be treated for this infection unless clinical or roentgenographic studies indicate its presence or unless the serum reagin titer continues to increase after birth or to persist at significant levels into the third mouth. The one possible exception to this rule would be in those rare instances where adequate serologic and roentgenographic follow-up of the infant is not available and at the same time the mother is known to have early syphilis, inadequately treated prenatally Under such circumstances the infection of the infant is so likely (perhaps better than 95 per cent) that a period of observation before making a clinical diagnosis and instituting treatment hardly seems justifiable. Treatment should never of course, be withheld in the presence of clinically demonstrable congenital syphilis, because of the vagaries of the blood serum reagin titer

Ideally the offspring of syphilitic parentage should have a blood serologic test at birth, or within the first few days of life. If this is positive, and the facilities for determining serum reagin content quantitatively are available,

the test should be repeated at weekly intervals until its trend is determined, remembering that a reversal to negative does not exclude syphilis in every instance A six month follow-up is essential.

If the blood serologic test is negative at birth, when the mother is known to be syphilitic, the test should be repeated at the age of one month, two months and six months. Infants seronegative at six months may normally be considered to have escaped congenital infection. Infants first discovered without previous study to be seropositive after the age of two months, provided the test is properly checked and interpreted, may be considered to have syphilis.

The collection of the blood of a young infant for the blood serologic test when left to the inexpert may prove a bar to the adequate use of the test. In the large majority of cases the superior auricular external jugular or antecubital arm vein (using a 24 gauge ¾ inch needle in the last instance) can be used as in arsphenamine injection (syringe technic) or enough blood can be milked from a deep stab in the heel with the obturator of a small trocar or a lancet (Chapter VIII) for the performance of the test. Blood from the longitudinal sinus or internal jugular may be obtained by the experienced, but these methods are rarely if ever called for and are not recommended.

Clinical Picture of Early Infantile Prenatal Syphilis.—Few children have outspoken signs of syphilis before the third week after birth, although eruptive lesions are common in the stillborn syphilitic infant. The sooner the symptoms appear the more serious the prognosis. Sylvester showed that the most critical and usually fatal cases appear before the fifth week or after the second month, so that prenatal treatment of the mother offers the best hope of reducing the early mortality Snuffles and cutaneous lesions are the commonest mode of onset, though an increasing irritability and restlessness with causeless crying and screaming when the child is laid down or handled may first be noticed. As the nose becomes obstructed nursing becomes difficult and loss of weight ensues, though the good state of nutrition of many syphilitic infants is cause for remark. The appearance of "hacking" or fissuring of the lips (Fig. 809) and an eczematous impetiginous syphilid at the angles of the mouth, whose scars form the rhagades, with mucous patches, condylomas at the anus, enlarged spleen and bone lesions, complete the most characteristic features of the picture The liver is seldom markedly enlarged The aphonic cry is quite characteristic The classical description of the marasmic syphilitic infant, with pot belly withered skin of a *café au lait* color old man facies ("keystone or old horse" face) and syphilitic pseudoparalysis of Parrot, is most often seen in the premature infant and the early severe types. Many children with perfectly typical eruptions, visceral and blood findings, seem only slightly underweight and well formed. Jeans and Cooke in studying the chief complaints which led parents to bring syphilitic children under two years of age for examination found in 610 cases, 230 nonsyphilitic complaints. The syphilitic complaints ranked as follows skin rash rhinitis bone lesions, request for a Wassermann test neurosyphilis eye lesions. Compare our experience with later cases.

Marfan describes as almost pathognomonic, pemphigus of the palms and soles, persistent snuffles with seropurulent discharge crusting and bleeding, chronic splenomegaly cutaneous syphilids, and Parrot pseudoparalysis. Ingraham (1935) found that from purely clinical study of the infant born of partially treated syphilitic mother the diagnosis of syphilis, has the disease is present, cannot be made with any degree of certainty in the *first two months of life*.

in as many as 5 per cent of cases. Definite obstruction to nasal breathing, almost always a symptom of congenital syphilis when it occurs in the first few days of life was actually present in four cases, at the time of birth. Syphilitic skin lesions and clinical osteochondritis were never present at the time of birth and approximately 3 per cent showed such manifestations early in life.

Wile and Mundt (1948) dealing with material up to two years of age, found that 45 per cent were brought to the hospital because of symptoms referable to syphilis; 33 per cent were referred because of positive blood tests, 20 per cent came because of entirely unrelated conditions and 2 per cent were detected in routine physical examinations which included blood tests. Stigmas in addition to the positive blood test were present in 82 per cent, but 56 per cent of the infants appeared healthy and apparently felt well on admission. Active cutaneous lesions were present in 27 per cent; in 19 per cent they were sufficiently characteristic to be diagnostic. About one fifth of the infants were distinctly underdeveloped, emaciated or actually marasmic.

Howles (1930) in a series of 100 infants less than three years of age (73.6 per cent Negro) lists the frequency in per cent, of some of the more important signs of early congenital syphilis as follows Skin and mucous membrane lesions 45 enlarged liver 25.2; rhinitis 24.2 enlarged spleen 20.3; clinically diagnosable chondro-epiphysitis 8.7; pseudoparalysis of Parrot and dactylitis each 1.9

The Cutaneous Lesions.—The outstanding dermatological features of the infantile cutaneous syphilids are in keeping with their general resemblance to the acquired secondary eruption. The most distinctive feature is a striking



Fig. 794 —Note the lesions about the face and mouth, the palms and legs, and the comparative freedom of the trunk in this heredosyphilitic infant. (Collection of Dr William Allen Pusey)

tendency to involve the chin and circumoral region the palms, the soles, and the anogenital region (Fig 794) An eruption which affects all these sites at once is extremely likely to be a syphilid. The macular syphilid is less common than the indurated papule, though the eruption may be macular on the body becoming, as in secondary syphilis, papular on the face and about the thighs and buttocks. The pemphigoid syphilid, with blisters or vesicles on the palms and soles, is relatively uncommon (Fig. 797) though highly diagnostic, and is interpreted as an unfavorable sign. Welde noted pemphigus in 12 per cent of his patients. The palmar and plantar surfaces are usually red and distinctly infiltrated, and may exhibit fissures (Fig 795) Irregular desquamation is the rule, but the merely desquamating palm or sole is hardly sufficient for a diagnosis alone. Pustular syphilids are rarely seen.

Differential Diagnosis.—*Eczematous* ulceration and *secondary infection* may at times produce a highly confusing picture about the buttocks, but the ensemble of regions involved usually makes the diagnosis. It is seldom safe to diagnose syphilis by erythematous lesions about the buttock alone unless indubitable condylomata with positive darkfield findings are present, for the so-called "napkin erythema" may occasionally (Fig 798) produce a corymbose

or grouped arrangement of definitely indurated papules on an erythematous base that is quite deceptive Nor is every erythema of the plantar surface to



Fig. 795 —The desquamating soles and grouping of lesions about the buttocks and genitalia in the heredosyphilitic infant. (Collection of Dr William Allen Pusey.)

be regarded as a syphilid for a very persistent plantar erythrodermia is occasionally seen as a nevus in infancy Changes in the hair are not character-



Fig 796 —The copper-colored spot conception in the diagnosis of cutaneous pigmented syphilids occasionally leads to interesting errors in diagnosis. This baby four months of age was covered with an eruption described by the medical examiner:

"Macular copper-colored syphilid over entire body Indurated plaques on skin of chest and on chin. Vesicular eruption on palms and soles. Spleen down 1.5 cm. Diagnosis: lues hereditaria."

This is an entirely satisfactory description of the eruption as such, the error being in the interpretation of copper-colored spots as diagnostic of a syphilid. The secret of the diagnosis here consists in the effect of irritation on the individual lesion. On stroking, pinching, or slapping the skin there was an immediate response from the pigmented patches in the form of urticarial wheals, limited to the pigmented areas. This is distinctive of the condition known as urticaria pigmentosa, which may come on very early in the life of the child (in this case at the age of one month). Other considerations speaking against syphilid are the child's general well-being, and the tremendous extent and uniformity of the eruption, which had not changed in three months. The serologic reaction on both mother and child was negative Urticaria pigmentosa has no known relation to syphilis.

istic, and the onychia sometimes seen may be well simulated by impetiginous infections. Even the highly characteristic "hacking" or rhagades (Fig. 800)

are occasionally simulated by eczematous fissures and secondary infection about the mouth (Fig 808) The exfoliative dermatitis of infancy (Ritter's disease) due to a staphylococcus septicemia, is sometimes mistaken for a



Fig. 797 —Syphilitic pemphigus of the soles. (Collection of Dr P C. Jeans.)

syphilid in the first few days of its course. This eruption usually begins on the trunk, extending as a bright erythematosquamous rash, and usually becoming confluent, with occasionally pustular and furuncular elements. It is



Fig. 798.—Papular lesions associated with "napkin erythema" and suggesting papular syphilid. The lesion disappeared in three or four days with an alkaline wash and dusting-powder.

superficial and without induration, advances more rapidly than a syphilid, and shows no special tendency to localize on the face, buttocks or palms, and soles at the outset, though they may be involved later The mucous membranes are seldom involved but may present a grayish membrane or a dry lividity

Impetiginous bullae may appear and the spleen be slightly enlarged. The infant may be febrile, and the disease progress rapidly to a fatal outcome. The vivid red of the acute dermatitis is in marked contrast to the indolent



Fig 799 —Papular lesions of miliary cutaneous tuberculosis in child. The distribution and ... ppearance suggest papular syphilid. The condition is rare.

brownish red of a syphilitic eruption Psoriasis does not occur in infancy The severer types of ecthyma produce ulcerative lesions which are rare in infantile syphilis and practically always associated with evidence of secondary



Fig 800 —The "hacking or 6 suring of the lip regarded as very characteristic early sign of heredosyphilis. Produced by cracking of the infiltrated skin and vermilion border

pyogenic infection, such as pustules and furuncles. Annular lesions are sometimes striking

Nose and Throat.—Snuffles is more diagnostic if hemorrhagic or purulent, although Findlay says mild forms are seen. Mucous patches as typical as any

seen in adults may be found at the commissures of the lips, and fissures and ulcers of the tongue and pharynx occur though rarely

Skeletal Involvement—Osteochondritis and Chondro-epiphysitis.—The first symptomatic warning is a flaccid paralysis if the lesion be in the upper extremity (humerus most often) or a spastic paralysis if in the lower extremity (Findlay) Parrot's pseudoparalysis, as this is called, may simulate Erb's



Fig 801—Rhagades and hacking (scars) produced by infiltrative and erosive syphilids about the mouth and chin in infancy

palsy The child cries when handled, and although no gross lesion may be seen it may often be palpated as a swelling at the end of a long bone All the characteristic bone lesions of acquired syphilis, plus dactylitis, more frequent in infancy may appear. Wile and Mundt (1042) found active bone lesions in 5 per cent of their infantile group The roentgenogram should be employed if there is any doubt as to diagnosis. The characteristic epiphyseal lesion is a



Fig. 802.—An ecthymatous fissuring of the lip, not due to syphilis, but to staphylococci.

thickening and irregularity of the epiphyseal line In advanced cases the line is replaced by a zone of fatty degeneration and necrosis between epiphysis and diaphysis which shows yellow in the cut specimen (Fig 803) Periosteal lesions and osteomyelitis and osteitis may be associated. The presence of cranial lesions is unusual. Craniotabes, the thinning of the central margins of the occipital and parietal bones with indentation on pressure is suggestive but not diagnostic of syphilis. Jeans and Cooke believe most of the skull changes

are rachitic. The deformity produced by a prolonged gummatous destruction of the septum differs not at all from that seen in late syphilis, but should be differentiated from the milder type with uninvolved septum seen as a developmental stigma in the heredosyphilitic facies, and shared with such conditions as oxycephaly and congenital ectodermal defect (Fig 839) Nonsyphilitic nasal suppurations may produce pictures suggesting the saddle nose of gummatous osteochondritis of the septum.

Roentgenographic Diagnosis of Infantile Congenital Syphilis.—The fact that widespread roentgenographically demonstrable epiphyseal and periosteal lesions of the bones, even in clinically normal children may occur in the first few weeks of life when congenital syphilis is present, has led to universal use of the roentgenogram in recent years for diagnostic purposes, in the apparently

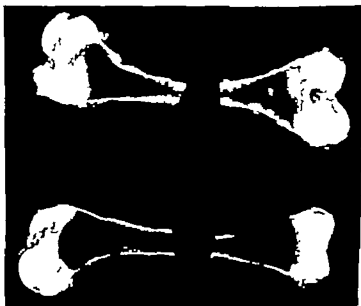


Fig 805.—Comparison of the ends of a normal and syphilitic femur in infants dying shortly after birth. The upper bone shows the irregular wavy epiphyseal line and the light (yellow) zone of fatty degeneration bet een epiphysis and diaphysis, seen in syphilitic chondro-epiphysitis.

healthy offspring of syphilitic mothers. The nature of these lesions is described in detail in the chapter on syphilis of the skeletal system

In applying this knowledge to clinical diagnosis, it is necessary constantly to bear in mind that the majority of these changes, particularly in their early stages are not diagnostic of syphilis, but may be produced by a variety of conditions (Chiari, 1938 Evans, 1940) Even prenatal therapy with bismuth, through producing areas of increased density in the shaft of the long bones close to the epiphysis, may cause confusion for the inexperienced (Caffey 1937 Christie, 1939 Whitridge 1940)

Fortunately the various conditions which Caffey (1939) has so admirably described as confusing the diagnosis of syphilitic osteochondritis (erythroblastosis, familial hemolytic anemia, and various forms of bacteremia, such as pneumococcic septic hemolytic and tuberculous) are sufficiently uncommon and are not often seen among the offspring of syphilitic mothers during the first few weeks of life. For accurate interpretation of the roentgenogram



A — Normal | B — Congenital Syphilis | C — Rickets | D — Bismuth Line

Fig. 804.—*Radius and ulna in early infancy to illustrate diagnostic value of roentgenographic demonstration of syphilitic osteochondritis. A,* Normal infant six days old. At this age the epiphysis (1) is radiotranslucent. The metaphysis (2) the first visible portion of the bone appears as a very narrow uniform band of increased density (temporary zone of calcification). The submetaphyseal area (3) and the diaphysis (4) are of uniform density with the normal trabeculation of the bone faintly visible. The periosteum is smooth. *B* In *congenital syphilis* the temporary zone of calcification in the distal metaphysis (2) of the radius and ulna illustrated is thickened and characteristically jagged (saw toothed) in appearance. The submetaphyseal zone (3) is rarefied from decreased calcium deposition as the bone grows in length and tongues of calcification extend into the rarefied zone from the diaphyseal side (4) The width of the rarefied zone indicates roughly the duration of the intrauterine infection. The illustration is from a three-week-old infant. *C*, In *rickets* the metaphysis is cupped (2) and the temporary zone of calcification is not definitely demarcated. Normal trabeculation is not clearly visible but there is no zone of submetaphyseal rarefaction. Periostitis (5) is visible along the shafts of the bones. Rickets generally makes its appearance at a more advanced age than does syphilitic osteochondritis. The illustration is from a 8½-month-old infant. *D Bismuth* therapy given to the mother close to term causes an area of increased density in the metaphysis and in the submetaphyseal area, sometimes extending deep into the shaft of the bone if bismuth is given throughout the latter months of pregnancy After birth, as the bone grows in length, the osseous tissue which is laid down in the submetaphyseal area (3) appears rarefied in contrast to the denser area or "bismuth line" (6) just proximal to it which has been caused by the antepartum bismuth therapy This change may usually be differentiated from syphilitic osteochondritis by the fact that the areas of increased density and of apparent decreased density are perfectly uniform, whereas in an infectious process like syphilis the decalcified areas are irregular The illustration is from a ten-day-old infant whose mother received a course of eight weeks of bismuth therapy the last injection being given thirteen days before delivery (three weeks prior to the taking of the roentgenogram)

it is, in our experience, critically essential that the roentgenologist consider in addition to the general physical status of the infant and the amount and duration of heavy metal therapy given to the mother prepartally the exact age of the infant being studied We emphasize this last point in particular because in the majority of instances, by the time an infant with congenital syphilis, who of course has usually been infected some days or weeks prior to delivery reaches the age of six weeks, there can usually be little doubt as to the nature of the osteochondritic changes. Most of the other conditions to be



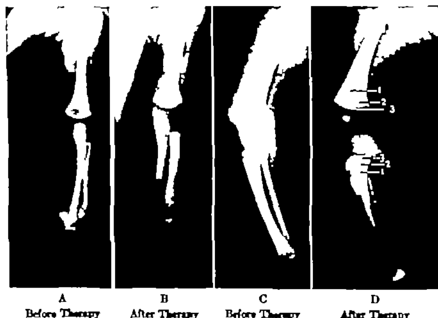
Fig 803 —Radius and ulna (A) and femur (B) from five-month-old infant with congenital syphilis. The roentgenogram shows a marked periostitis of all the long bones, in several layers on the outer aspect of the femur which is particularly characteristic in appearance in this location The osteochondritic changes seen earlier tend t heal as the periost tis ppears. Periostitis is seldom present at the time of birth and is rarely demonstrable until the infant is several weeks old. It likewise tends t heal spontaneously provided the infa t survives and is a less characteristic finding in the second than in the first six months of lif

confused with syphilitic osteochondritis, on the other hand, being acquired postnatally rather than prenatally develop at a somewhat later period in the infant's life (two to three months) and at this more advanced age show a type of early osteochondritic change that is usually demonstrable in congenital syphilis during the first month postnatally

Our experience has been in conformity with that of Black (1939) to the effect that the existence of unequivocal osseous syphilis roentgenographically demonstrable in the presence of negative serologic reactions when the better serologic technics are employed, is extremely uncommon. It may occasionally

occur however as observations like those of McCord (1038) have shown, in which not only the abnormal roentgenogram but *Spirochaeta pallida* as well was demonstrable in seven *infants with negative results to serologic tests.* (*Cf* also Ingraham 1935)

The roentgenogram has its **greatest** diagnostic value in early infancy up to the *age of six or eight weeks, during the period when serologic testing may* still leave uncertainties. It should be routinely employed as an adjunct to serologic diagnosis in those infants who appear healthy at the time of birth



A Before Therapy B After Therapy C Before Therapy D After Therapy

Fig. 606.—Effect of antisyphilitic therapy in healing early congenital osseous syphilis. *A*, Pathologic fracture of the radius in three-week-old child, as result of mild trauma to grossly diseased bone. Note in the distal metaphysis the jagged band of increased density with spur on the distal radial metaphysis. *B* The bone has healed normally after splinting and two months of sulpharsphenamine intramuscularly *C*, Marked syphilitic osteochondritis in six-day-old infant. Note jagged metaphyseal line and irregular band of subepiphyseal rarefaction in the distal metaphysis of the femur and in both the proximal and distal metaphyses of the tibia. *D* After two months of treatment the rarefied area (*1*) has receded onto the shaft and is gradually becoming denser as the bone grows in length. Just distal to this rarefied area is ide band of increased density (2) in contrast to which the tip of the bone next to the metaphysis (3) appears rarefied. This band of increased density results from bismuth therapy given the infant. The bone at the end of the shaft is of normal density This infant received five eeks of bismuth therapy and was then placed on sulpharsphenamine

though their blood tests are positive. Only unequivocal multiple osteochondritis (or periostitis) should be accepted as diagnostic. Doubtful or suggestive signs should be completely gnored as absolute diagnostic criteria, or as a basis for commencing treatment. Instead the infant should be restudied roentgenographically in two to three weeks for evidence of progression of the lesion or for the development of a more characteristic picture. A progressing osteochondritis which may occasionally be accompanied by a periostitis, occurring in a seropositive infant during the first six weeks of life may be considered as establishing a diagnosis of syphilis

Ingraham, Shaffer Spence and Gordon (1941) have shown that early diagnostic errors (before the age of two months) usually arise from too close reading of the roentgenograms, which tend to place too much significance on minor changes without adequate knowledge of so-called "normal variations," or from misinterpretation of the densities produced by antenatal therapy. Later diagnostic errors (*i. e.*, after the age of two months) from the roentgenographic standpoint result almost invariably from confusion caused by the periosteal changes often associated with developing rickets. Periostitis in the seronegative offspring of a syphilitic mother is more apt to develop into frank rickets than into advanced *infantile syphilis of the bone* though we have seen occasional cases in which the initial periostitis disappeared without either of the courses just mentioned being pursued.

The roentgenogram should not be used as a routine diagnostic procedure on all infants born of syphilitic mothers, but only in selected cases. Our Philadelphia General Hospital experience has shown the roentgenogram to be of some positive diagnostic value in 27 per cent of cases in which the mother had had no prepartal treatment, in 10 per cent of cases in which she had had less than two months and in no instances in which as much as sixteen weeks of prepartal treatment had been given.

Hemorrhagic Disease.—Syphilis is one of a variety of causes of melena neonatorum and was observed by Thomsen in 9 of 100 autopsies on children born alive of syphilitic mothers. The

Fig. 507

A SUMMARY OF THE CHIEF SYMPTOMS OF INFANTILE HEREDOSYPHILIS

The Eruption Rare before the third week, distribution distinctively to the face and mouth region, the anogenital region and the palms and soles macular maculopapular, secondarily eczematous, and often infected. Condylomas and mucous lesions. Pemphigoid bullae 10 per cent Infiltrations of lips, face, palms and soles.

Snuffles As common as the eruption and as early May be mild and not distinctive. Almost diagnostic if hemorrhagic.

Hacking of the Lips Fissures, especially of the upper lip and the middle of the lower.

Rhagades Infiltrative fissures, eczematous involvement of cheeks and chin near the commissures.

Enlarged Spleen Almost diagnostic before the fourth month (60 to 70 per cent present).

The Cry Cracked and aphonic Very suggestive.

Pseudoparalysis Flaccid of the upper extremity spastic of the lower presumably due to painful movement, but may be neuritic due to osteochondritis and epiphysitis.

Osteochondritis, Chondro-epiphysitis, and Osteomyelitis: Palpable enlargement and tenderness of the ends of the long bones, single or multiple, oftenest the upper extremity May be fusiform involvement of shaft.

Epitrochlear Adenopathy in the Newborn Stressed by some writers.

Saddle Deformity of Nose The sequel of the osteitis and gummatous changes in snuffles.

Pulmonary Hepatic, Marasmic Symptoms less common.

syphilitic infection according to Neumann is accepted at the present time as the cause of an abnormal susceptibility to septic infection rather than the actual directly responsible factor in the hemorrhagic diathesis. Lambkin describes the various local lesions such as ulcers, condylomas, etc., which may cause bleeding from the rectum in children.

Miscellaneous Symptoms.—Eye lesions are infrequent in infancy (Jeans and Cooke). Wile and Mundt (1912) found chorioretinitis in 3 per cent, optic atrophy and extraocular paralyses in 1 per cent each in children under two years. Fever is common, rarely above 101° F and disappears quickly with treatment. *Nephritis* occurred in 10 per cent of the heredosyphilitic children of Welde series The acute parenchymatous nephritis of heredosyphilis is a rarity in our experience as in that of Jeans and Cooke and like that of acquired syphilis, requires corroborative evidence of syphilis and a positive therapeutic test for diagnosis. In the only case under J.H.S.'s observation on Wile service the hemorrhagic pyonephritis, for such it microscopically cleared up rapidly when the child was placed on mercury by mouth and neoarsphenamine. Renal disturbance did not occur in Wile and Mundt (1912) series. Fink *Icterus*, Carpenter (quoted by Findlay), and Findlay have seen cases Varying grades of anemia in infants are attributed to syphilis, but are evidently not common Chiaravalloti found the hemoglobin in 130 cases to range from 11 to 73 per cent. Nitschke found no evidence of any uniform change in 30 children except a slight tendency to lymphocytosis. *Splenic anemia*, while at times ascribed to syphilis, does not seem to bear a distinctive relation to the disease *Icterus neonatorum*, according to Findlay is very rarely syphilitic in origin. Peritonitis and ascites are rare complications, examples of which are described

by Acuna and Casaubon and Spence and Tittle Orchitis develops in the first few weeks of life, according to Findlay in 2 to 3 per cent of cases. Meningitis, of syphilitic origin, is considered under neurosyphilis in childhood. Pulmonary symptoms may rarely arise from syphilitic changes in the lungs, and P Jares believes he has seen 3 genuine cases in the first week of life. Marasmus proved to be associated with positive blood Wassermann reaction in only 8 per cent of Findlay cases, but Barbier describes type of general trophy of the tissues associated with Parrot pseudoparalysis which he thinks is syphilitic in origin.

Increased blood sedimentation rate, in active congenital syphilis, observed by György (1931) has been restudied by Ingraham (1935) Rarely will the blood serologic test be negative when this test is positive and Weiss (1925) has shown that the rate is not much increased until the disease becomes clinically manifest.

Fig. 808.

THE LANDMARKS OF TARDIVE HEREDOSYPHILIS

Major	Secondary	Minor	Debatable.
Positive blood serologic reaction.	Frontal bosses.	Venous ectasia.	Carabelli tubercle.
Interstitial keratitis.	Aplasia of incisor teeth.	Hypertrichosis.	Retromastoid adenitis.
Hutchinsonian incisors.	Scaphoid scapula.	Ulnar deviation of middle fingers.	Persistent infantile hydrocele.
Mulberry molars.	Marked enlargement inner third of clavicle (old osteitis) (Higoumenakis sign.)	Constitutional subnormality	Hypertrophic thymus and thymic abscess.
Eighth nerve deafness.	Disturbance of age development ratio.	Backwardness.	Alopecia areata in children.
Saber tibiae: Osteitis. Periostitis. Simple hypertrophy	Precocity and high nervous irritability	Hypertrophic frontal suture.	Knock-knee elbow
Osteitis of the nasal septum Snuffles. Saddle bridge.	Early epitrochlear adenopathy	Craniotabes.	Absence of the xiphoid process.
Splenomegaly	High narrow palatine arch.	Bilateral dacryocystitis in childhood.	DuBois little finger sign.
Rhagades and scars.			
Early dactylitis.			
Facies.			

Strongly presumptive or diagnostic.
Insufficient for diagnosis alone.

Landmarks of Tardive Heredosyphilis Differentiation of Syphilids and Developmental Dystrophies.—A rough classification of the earmarks of heredosyphilis into syphilids, caused by the presence of *Spirochaeta pallida* in the lesion or tissue affected and developmental or structural anomalies resulting from the syphilitic intoxication, has great value as a guide to clear thinking (Fig. 808) Developmental anomalies may be the product not only of the action of the syphilitic intoxication if such a term may be used, upon the dystrophic structure as such but also upon the growth centers or organs of systemic importance to the growth centers, such as the endocrine glands. Both syphilids and dystrophies are likely to appear in any case in which the infection has been present during uterine and early infantile existence.

From time to time new developmental abnormalities are proposed for consideration as signs of "heredosyphilis, in some instances in the more or less distant ancestry of the patient. Many

of these are parts of the French conception of syphilitic dystrophies (syphilis héréditaire tardive). These debatable signs have been listed as "suggested but unestablished," and no attempt has been made to insure the completeness of the list. Individual impression and experience will always influence decisions on these less significant points. The minor sign is at best merely suggestive and carries no weight alone.

Such a classification cannot, of course, meet with complete acceptance in its details or be all-inclusive, but it serves the purpose of a general impression of relative importance. In Fig. 809 the symptoms and signs of congenital and heredosyphilis are classified on the basis of true syphilids and developmental changes.

Fig. 809

SYPHILIDS AND DEVELOPMENTAL STIGMAS

Syphilids.	Developmental Stigmas.
Positive blood Wassermann reaction.	Facies.
Eruptive lesions:	Dental dystrophies.
Skin.	Age-development ratio disturbed:
Mucous membranes.	Delayed dentition.
Keratitis.	Delayed menstruation.
Early splenomegaly.	Oversize and undersize.
Osteitis:	Gigantism.
Septum.	Dwarfism.
Tibia.	Bosses.
Clavicle.	Scapulae.
Dactylitis.	Some tibiae.
Chondro-epiphysitis.	High arched palate.
Periostitis.	Ulnar deviation.
Bilateral hydrarthrosis.	Venous ectasia.
Dacryocystitis.	Hypertrichosis.
Rhagades.	See also "syphilis héréditaire tardive."
Gumma.	
Visceral syphilis.	
Neurosyphilis.	

THE GENERAL SYMPTOMATOLOGY OF TARDIVE HEREDOSYPHILIS

The age of incidence of symptoms of tardive heredosyphilis was given by Fournier (212 cases) as three to twenty-eight years, with a mean of twelve years. Our own experience includes more than tardive cases. The older patients were usually recognized by stigmas and sometimes presented symptoms which responded to treatment. It is rare to find active manifestations after thirty.

Figure 810 summarizes in order of frequency the lesions and stigmas presented by the most important case series extant. The overwhelming preponderance of eye lesions, which exceed even the positive blood serologic reaction in frequency, in marked contrast to infantile prenatal syphilis, points both to the field of diagnostic and suspicion-arousing clues, and to the social and economic importance of tardive heredosyphilis. The hutchinsonian triad, formerly much emphasized in diagnosis (interstitial keratitis, hutchinsonian teeth and eighth nerve deafness), is now recognized as a rarity in its complete form.

Why the Tardive Syphilitic Child Seeks Medical Advice.—The chief complaint is frequently the deciding factor in a diagnosis, and its analysis

Fig 810.

RELATIVE PERCENTAGE FREQUENCY OF SIGNS OF LATE CONGENITAL SYPHILIS ACCORDING TO VARIOUS AUTHORS

Signs	Stokes (1946)	Jeans and Cooke (1930)	Cole (CCG) (1937)	Howles (1939)	Wile and Mundt (1942)
	298 cases	707 cases	1010 cases	147 cases	402 cases
	Per cent	Per cent	Per cent	Per cent	Per cent
Eye lesions (total)	78	51	46.5	45.0	59
Interstitial keratitis	54	27.3	20.9	38.7	44
Bones	44	—	—	29.9	64
Saber shins	43	—	—	—	34
Characteristic teeth	32	10.7	—	16.1	31
Saddle nose	30	2.3	—	21.7	10
Neurosyphilis	26	—	13.9	—	27
Facies	21	—	—	21.7	—
Scaphoid scapula	20	—	—	12.9	27
High palatine arch	19	—	—	13	32
Liver enlarged	19	—	2.7 total visceral	10.1	1.2
Spleen enlarged	14	—		15	1.2
Epiphysis enlarged	13	—	—	15	—
Deafness N.VIII	10	1.5	5.2	8.1	6
Rhagades	6.5	5.0	—	2.9	5
Gumma, nose throat	6	2.1	—	2.0	—
Thickened clavicles	4	—	—	—	—
Hydrarthrosis	3	—	—	—	2
Periostitis (active)	3	—	—	—	3
Dactylitis	2	—	—	—	2
Active skin or mucous membrane lesions	—	2.4	5.6	17.6	2.5

points to the medical groups which have the best opportunity to identify the heredosyphilitic child.

General ailments lead (32 per cent) with eyesight 24 per cent, ear, nose, and throat 22 per cent, syphilological follow-up 14 per cent, and neurosyphilis 8 per cent.

The general ailments which include 32 per cent of the chief complaints, exclusive of symptoms suggestive of nervous derangement, are as follows:

In the history of childhood ailments, 29 per cent could be interpreted as definitely syphilitic in origin and 27 per cent as questionable. The remaining 44 per cent were obviously nonspecific. In Wile and Mundt's (1942) series half of the group sought hospital care because of symptoms referable to syphilis. Interstitial keratitis was the principal diagnosis on admission in the largest number of patients, central nervous systems syphilis next most frequent, followed by bone and joint disease. The diagnosis of 86 per cent of the patients could be made on the presence of one or more characteristic stigmas, with or without a positive serologic reaction. The so-called "congenital syphilitic facies" was observed in more than one-fourth of the patients and 9 per cent had obvious symptomatic central nervous system syphilis.

The Blood Serologic Reaction in Tardive Prenatal Syphilis.—Speaking from the diagnostic standpoint, the blood serologic reaction ranks lower in the recognition of tardive heredosyphilis than it does in many other forms of syphilis, and contrasts markedly with the 100 per cent estimate of its value

Fig. 811

MISCELLANEOUS COMPLAINTS IN SYPHILITIC CHILDREN

General Complaints.		*Ear, Nose, and Throat.*		*Nervous System.*	
Arthritis	18	Deafness	20	Convulsions	6
Abdominal symptoms	3	Nasal obstruction	11	Mentality	5
Physically retarded	2	Cervical glands	6	Paralyses	4
Gait	2	Perforated palate	3	Nervousness	3
Never talked	2	Nasal deformity	2		
Nephritis	2	Nasal discharge	1		
Hematuria	1	Sore throat	1		
Asthenia	1				
Feminism	1				
Alopecia totalis	1				
Esophageal obstruction	1				
Osteomyelitis	1				

after the first two or three months of infancy. The blood serologic reaction, positive in the aggregate in only 60 per cent, follows an even more pronounced age gradient toward the negative, than does that in the acquired form of the disease. In the first decade its efficiency approximates 88 per cent, in the second 63 per cent, in the third, 46 per cent; in the fourth (over thirty years), 15 per cent. After twenty years of age, more than half the cases are identified by clinical signs.

The Eye Lesions of Tardive Prenatal Syphilis. Interstitial or Parenchymatous Keratitis.—Fifty two per cent of all persons who are brought to medical attention because of heredosyphilis have or have had interstitial keratitis, and only 22 per cent have entirely normal eyes, according to our experience. Figure 812 seems to accord with the importance assigned them in the literature. Lennarson and Jeans (1937) found 45 per cent interstitial keratitis, 15 per cent chorioretinitis, and 6 per cent optic atrophy and Wile and Mundt (1942) 44 per cent interstitial keratitis, 10 per cent chorioretinitis, and 3 per cent optic atrophy in a similar type of material. For the syphilitic child interstitial keratitis thus becomes one of the most serious and distressing

of symptoms. It involves, even in the mild case, a period of absence from school, and of photophobia and discomfort that leaves a permanent impress on the patient's mental organization. Untreated or poorly treated it leaves a residue of actual damage to vision estimated by Igersheimer at 40 per cent of all patients affected, by Cole *et al.* (1937) at 27 per cent and by Klauder and Vandoren (1941) at 19 to 22 per cent. Interstitial keratitis constitutes from 0.4 to 0.6 per cent of all eye disturbances as estimated by Derby and Walker (77 000 eye cases) and Hoor (375 000 eye cases).

The onset of interstitial keratitis is commonly between the ages of five and sixteen though it may appear for the first time as late as thirty. In an analysis of 542 cases Klauder and Vandoren (1941) found that 15 cases developed interstitial keratitis before the age of three years and 8 cases after the age of thirty years. The statistical curves of Cole *et al.* (1937) show that a patient with late prenatal syphilis is in constant danger of developing interstitial keratitis up to the age of twenty to twenty five years. It is more common in girls than boys. The predisposing factors include lowering of general resistance, such as is produced by a sudden severe chilling, an attack of grippe



Fig. 818.

or in one or two of the late cases we have seen, a pregnancy which one would rather expect to have the opposite effect. Dietary deficiencies in particular *ariboflavinosis may play a secondary role* (Takeda, *1934*, Kruse *et al.*, *1940*, Sydenstricker Kelly and Weaver 1941 Woods, 1943). Our experience with the treatment with riboflavin of a limited number of cases of interstitial keratitis, who did not respond well to antisyphilitic therapy at the Philadelphia General Hospital, has been disappointing, no alteration in the normal course of the disease being noted. The condition preserves an unaccountable independence, and may come on during a course of quite intensive mercurial treatment, or from an absolutely clear sky in patients almost devoid of stigmas, and certainly without the slightest evidence of impairment of general health. It may also appear for the first time following the institution of treatment in an asymptomatic patient. Interstitial keratitis occurs rarely in the secondary period of acquired syphilis and in association with chancre of the eyelid (Pariser 1939). It is, however so overwhelmingly an accompaniment of late prenatal syphilis that its diagnostic value is paramount and should be impressed on the student from the outset.

Symptoms.—The earliest symptom is slight ciliary congestion followed by the appearance of small grayish infiltrative deposits either toward the periphery or in the center of the cornea. The inflammation involves the entire thickness of the cornea, the grayish deposit being lymphocytic. Ulceration rarely occurs (deSchweinitz) Circumcorneal injection of the sclera, suggesting an episcleritis, may be the first sign that attracts the patient's attention, or there may be a slight smarting, lacrimation and discomfort in the light, the forerunner of the intractable photophobia from which these patients suffer (Fig 813) When the patient is first seen by the physician, varying degrees of clouding of the central portion of the cornea with impairment of vision, have usually developed and capillary loops have begun to extend in from the



Fig 813.—The photophobic element in typical heredosyphilitic facies. Note the nebula over the right cornea. The process had been reduced to practical inactivity by treatment, but the photophobic habitus persisted.

limbus vascularizing the affected area. Marked degrees of vascularization and opacity produce the so-called "salmon patches" of the more severe cases, with their yellowish-red dull sheen The limbus becomes red and swollen in severe cases from the new formation of vessels.

The physician who will accustom himself to examining the cornea with a lens for cloudy spots and faint grayish stippling whenever a child complains of sore or running eyes, or has a "conjunctivitis" or "pink eye," will contribute inestimably to the diagnosis and perhaps the ultimately successful treatment of interstitial keratitis Even the protracted "cold" which cannot stand strong light is a proper object for a quick survey of stigmas and the taking of a blood serologic test

The infiltration and vascularization of the cornea are almost invariably accompanied by involvement of the iris and the anterior uvea, which accounts for increased pain and lacrimation, although these signs may be masked by the semiopaque cornea. In 700 cases of interstitial keratitis analyzed by Spicer (1924) only 6 per cent failed to show evidences of anterior uveitis Iritis was present in 28 per cent, cyclitis in 48 per cent and anterior choroiditis in 29 per cent (*cf* Wood, 1943) Synechial adhesions result, if the pupil is not dilated, and the iritis may leave pigment deposits on the posterior surface of the cornea. Secondary glaucoma may be a complication. Intractable episcleritis also occurs (John Lane)

Interstitial keratitis, in the older literature is always described as bilateral and as inevitably involving the other eye once it makes its appearance.

Preventing Involvement of the Other Eye.—There can be little question that the course of the condition in the second eye can be greatly reduced in severity and shortened in time by the use of the arsphenamines combined with heavy metal or if need be with fever and involvement of the other eye frequently prevented. Cole *et al.* (CCG 1937) found that among 64 patients with interstitial keratitis affecting one eye, the involvement remained unilateral in 41 (64 per cent) Klauder and Vandoren (1941) found that the chance of escaping bilateral involvement increases in direct ratio to the lapse of time from the onset of interstitial keratitis in the first eye. In 42 per cent of patients both eyes were involved either simultaneously or within one month of each other The percentage with second eye involvement increases slowly to the tenth year At this time the second eye has become involved in 79 per cent.

Guy brought out clearly the contrast between the older ineffective mercurial therapy and the results of modern treatment in this particular but the period of observation in his cases was short. Carvill and Derby reported on the joint efforts of the Massachusetts Eye and Ear Infirmary and the Syphilis Clinic of the Massachusetts General Hospital to make thoroughgoing treatment applicable to this situation Ith series of 388 cases treated with reasonable thoroughness. Among these it was found that the duration of the attack in the second eye is longer than in the first in only 25 per cent of cases, that intensive treatment may have some influence in preventing involvement of the second eye and in reducing the severity of the attack in this eye. In 18 per cent of 100 cases there was no involvement of the second eye. The proportion of recurrences in treated cases was only 3.6 per cent as compared with 27 per cent, 14 per cent, and Spicer 9 per cent. I 100 untreated cases Carvill and Derby observed 27 per cent recurrences, an overwhelming tribute to the value of systemic treatment. Semi-effective treatment, even with the arsphenamines, was not effective in preventing interstitial keratitis in the later years in 10 cases. In an important follow-up report by Carvill on this same series of cases she found that of the 18 per cent in whom intensive treatment had prevented involvement of the second eye, no involvement of that eye had subsequently occurred in 16 out of 17 cases reexamined to determine this question. The period of observation, more than five years in all cases, nine years or more in 12, would seem definitely to establish the fact that the effective use of modern treatment is capable of completely preventing, at least in some cases, the involvement of the second eye Osborne and Putnam also report success in preventing involvement of the second eye in 30 cases after treatment was started. It is, however known that many years may sometimes elapse between the first and the second attack. Klauder and Vandoren large series failed to provide convincing evidence that involvement of the second eye could be prevented by treatment as such, the time factors being more important.

Interstitial keratitis runs, as a rule, a self-limited course punctuated by relapse in untreated cases, the frequency being reduced by treatment as just noted. Hoor estimates the frequency under the old regimen at 18 to 22 per cent, Cole *et al.* (CCG 1937) at 29 per cent with poor treatment during the

acute stage Under proper treatment relapse may be reduced to 15 per cent (Cole *et al*) or even to 8 per cent or less (Klauder and Vandoren). We have seen the first attack and the relapse separated by as much as seven years of apparently complete good health. Each recurrence of course, adds to the damage done the cornea by vascularization and inflammatory deposits. Complete involution is not the rule at least some traces of vascularization persisting indefinitely in most cases, partly we believe because of delay in instituting treatment. Occasionally however the vessels may completely disappear Klauder and Cowan (1939) have however pointed out that with the use of slit lamp microscopy it is possible to make an almost certain diagnosis of a previous interstitial keratitis in nearly every case and after any length of time. It is, moreover usually possible to distinguish syphilitic from other forms of keratitis The value of utilizing this study to establish a congenital infection, even after many years, is emphasized. A negative examination is evidence that the patient has not had interstitial keratitis, but does not, of course, prove the absence of congenital syphilis. The nebula or opacity in, rather than on or behind, the cornea is quite characteristic when present. The impairment to vision is chiefly dependent upon the central location of the infiltrate and since this part of the corneal inflammation is the last to undergo resolution, it is impossible to tell, until the very end of the attack, what impairment, if any will result. Carvill and Derby found that 27 per cent of 200 children lost from a month to three years of school, 24 per cent were definitely handicapped in their work for a livelihood

The differential diagnosis of syphilis from tuberculous interstitial keratitis must be made by general signs. The presence of fine straight vessels extending in from the limbus is good evidence of old interstitial keratitis. The vessels in trachomatous pannus anastomose and are more superficial those of former ulcer are confined to the scar (deSchweinitz)

In taking the history of eye disturbances in childhood tuberculous keratitis should not be forgotten as a possibility in the eagerness to make a case for syphilis.

The remaining eye lesions, detailed in Fig. 812, are in no way distinctive of heredosyphilis, apart from their occurrence in childhood Extra-ocular paralyses and strabismus, chicken-track and sand-grain punctate pigmentary residua of peripheral or anterior chorioiditis, vitreous opacities and remains of uveitis in children should always be regarded with suspicion. Primary optic atrophy is said to be an unusually frequent accompaniment of juvenile tabes, but it is a much less frequent cause of failing vision in the prenatally syphilitic child than are chorioiditis and chorioretinitis. Chorioiditis is apt to follow interstitial keratitis, or be revealed as the involution of the corneal process permits inspection of the fundus.

The Ear Nose and Throat Symptoms of Heredosyphilis.—Kerald and Kemp confirm our observation of a 10 per cent incidence of eighth nerve deafness. Hutchinson found 15 per cent deaf among his cases. Their analysis showed the condition to be more common in males than females, which is at variance with other observers The age of onset approximates puberty but may be earlier It may be sudden or gradual and is usually accompanied by tinnitus and vertigo Interstitial keratitis was the most common associated lesion preceding or accompanying the deafness. The blood serologic test was positive in more than 90 per cent and the spinal fluid invariably negative Breitenstein describes, in addition a type which is annoyed by subjective

noses but has only slight impairment of hearing, and a severe antenatal involvement which gives rise to deafness from birth and consequent deaf mutism. In cases which progress to complete deafness before the tenth year mutism is likely to ensue. Beck and Schacherl describe serologically negative cases.

We have been impressed with the difficulty of basing a diagnosis of prenatal syphilis purely upon eighth nerve deafness in the child, without definite confirming evidence. In one family group, in which the youngest child was totally deaf, two sisters and the mother were found to present the same condition. The youngest child had classical frontal bosses, and the eldest a suggestive facies, but all were seronegative and presented no other stigmas. The fullest investigation of the parents failed to reveal anything. Such borderline cases certainly cannot be swept into the syphilitic category merely by the fact of eighth nerve deafness developing without infectious or toxic accidents in childhood.

Saddle Bridge and Nasopalatine and Nasopharyngeal Gumma.—The flattened bridge of the heredosyphilitic face is only in part due to actual



Fig. 814.—Saddle bridge due to gummatous osteitis of the nasal septum, with destruction of the septum and perforation of the palate in a patient with heredosyphilis. This is to be distinguished from the developmental dystrophy

destructive change in the bones. When such occurs it adds greatly to the worth of the nasal depression as a sign. In fact, high perforation of the nasal septum with collapse of the bridge and flaring of the nostrils, especially if accompanied by perforation of the hard palate, is as nearly pathognomonic of syphilis as any item in the category. The history of trauma is too readily accepted by plastic surgeons as explaining such deformities of the nose, for the trauma merely initiates the gummatous change in many cases. That not every flattened bridge is syphilitic is sufficiently emphasized by Figs. 839 and 840. Perforation of the soft palate (Fig. 815) is highly suggestive but not absolutely diagnostic.

Dangers of Operative Interference in the Nose and Throat.—The otolaryngologist has many opportunities to diagnose heredosyphilis by following to their source the dental dystrophies, depressed nasal bridges, septal perforations, and high palates, which pass before him. Nicolas, Massia, and Dupasquier believe that the incisor bud, from which the central part of the

upper alveolar process is formed is especially susceptible of attack by *Spirochaeta pallida*. Such a special *susceptibility* would seem to extend to the septum and palate in heredosyphilis, and makes the recognition of the underlying condition of the utmost importance before operative interference, either for obstructed breathing deflected septum or plastic restoration of a saddle bridge The type of saddle bridge which represents a developmental dystrophy (Fig 806) may conceivably sustain operative trauma better than one which depends on the destruction produced by an osteitis gummosa (Fig 814). Gummatous involvements of the jaw may be taken for alveolar abscess or

Fig 815 —Cicatricial deformity of the nasopharynx, the result of tonsillectomy performed upon patient with untreated heredosyphilis. The patient had characteristic facies, suspicious upper central incisor teeth, large liver and positive blood serologic test, none of which was recognized before the operation which resulted in permanent deformity

sarcoma in the lower and maxillary cyst or sarcoma of the antrum in the upper jaw and should invariably be checked by the blood serologic test and a search for stigmas. The larynx in severe cases of infantile heredosyphilis may show edema and ulceration (Still found 14 per cent) but in later years, apart from an occasional slight sclerosis of the cords, there are no distinctive laryngeal lesions.

Gummatous breakdown failure to heal and cicatricial distortion in the pharynx (Figs. 815 816) are more frequent consequences of tonsillectomy in heredosyphilis than is generally realized The incidence in our series amounts

EFFECT OF TREATMENT IN PREVENTING OBSTRUCTIVE CHANGES FOLLOWING TONSILLECTOMY

Treated before operation	[illegible]	[illegible] cases
Postoperative gumma	None	
Not treated before operation		[illegible] cases
Postoperative gumma	9 cases	

Fig 816.

to almost 20 per cent in the previously untreated cases while not one of those properly prepared by treatment experienced gummatous complications. Use of the blood serologic test and familiarity with the signs would prevent much of this irremediable damage

The Dental Abnormalities of Heredosyphilis.—The teeth provide the diagnostician with some of the most important clues to the recognition of heredosyphilis The tendency of the average observer if he considers the teeth at all in his study of the patient is to be too inclusive and too indefinite in his conceptions, and to rate as syphilitic a variety of dystrophies which have no

special connection with the disease. The abnormalities which suggest syphilis can be quite exactly defined, and have a rational basis in the embryogenesis of the dental structures.

The first point for the student to grasp is the fact that only the second dentition teeth show changes definitely characteristic of congenital syphilis.

Two groups of teeth whose embryonal anlagen are undergoing development and ossification in the jaw during late uterine and early infant life, bear the brunt of the stigmatization produced by syphilis. These are the upper central incisors of the second dentition, and the first or "six year" molars. The upper central incisors, when typically modified by the influence of the infection, become the so-called "hutchinsonian teeth," described by Jonathan Hutchinson in 1858. The six year molars which are developing in

SECOND DENTITION TEETH IN HEREDOSYPHILIS

130 cases

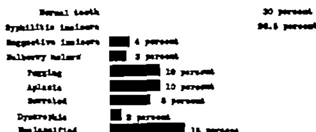


Fig 617

the jaw during the first year of the child's life present, on eruption, defective cusps which produce the appearance described as "mulberry molar "Moon molar" after the English surgeon (1884) or Fournier tooth."

The studies of Karnosh (1926) and the more recent work of Anderson (1939) Johnston, Anderson and McAleney (1941) and Stathers (1942) have indicated that the dental defects of congenital syphilis show wider range of variation than is generally known. This variation may range from complete failure of development of tooth to slight diminution in size and alteration in form. The difference is largely one of degree.

Dental stigmas are more readily recognized when the oral structures are viewed as whole. The incisors of the second (and occasionally of the first) dentition, the cuspids (canines) and the first molars are involved as group The most consistent physical characteristic of the dental malformations is the dwarfing of the entire tooth and lack of development of the premaxillary bone. The *lower central incisor* is involved much less frequently than the upper central incisor and the canines are seldom affected because these teeth usually develop somewhat later The permanent *upper lateral incisors* are rarely affected because they do not begin to develop until much later time (about 10 months)

In those cases in hich the onset of the disease has been early and severe enough to affect jaw development peculiar deformity appears known as the open bite. In differentiation from the open bite produced by thumb sucking and malnutritional disturbances, the open bite of congenital syphilis shows no contraction of the anterior region such as may produce overcrowding of the teeth, there is not the bent or distorted appearance of the alveolar process seen in the open bite resulting from habits, nor is there evidence of failure of proper dental eruption. In the open bite associated with congenital syphilis, the teeth as well as their supporting bony structure, appear to be wanting in sufficient substance to bring them into proper occlusal relations. Stathers found open bite to be present in 56 per cent of his 60 cases. The bite was normal in only 10 per cent; the teeth were edge to edge in 22 per cent, were slightly overlapped in 14 per cent and had *deep overbite in 10 per cent.*

Stathers also found that the *high narrow palatine arch*, which has often been described as characteristic of congenital syphilis is rare, and when found is usually associated with narrow

saddle arch. Stoll has emphasized this as a diagnostic sign. In our experience it is only occasionally seen and not in itself diagnostic.

The Deciduous Teeth.—Although it is generally conceded that there is no change in the deciduous teeth which might be considered characteristic of congenital syphilis, and certainly nothing which could be called pathognomonic yet, Brauer and Blackstone (1941) and Sarnat and Shaw (1942) have observed dystrophic changes which almost certainly seem to be related to this disease. The fact that the deciduous teeth are not more frequently affected is explained on the basis that this morphodifferentiation and dento-enamel junction are determined only in utero, usually before syphilis invades the fetal tissues.

Brauer and Blackstone found in 16 congenitally syphilitic children with deciduous central incisors still present, that 37 per cent had cupping or notching of the central lobe of these teeth in the incisal region. Two of the children had marked enamel hypoplasia of the posterior deciduous teeth.

Schour and Massler (1940) report that the deciduous central incisor has its initiation and histodifferentiation stage at approximately seven weeks in utero, that the apposition of the enamel and dentine begins at approximately four to four and one-half months in utero and that the crown of the tooth is five-sixths formed at birth. Since the last phase of incisal apposition takes place at the seventh or eighth month of fetal development, it is conceivably possible that apparent hypoplasia of the central lobe could be a manifestation of syphilis.

Sarnat and Shaw found that in each of four instances when roentgenograms revealed characteristic hutchinsonian incisors in unerupted teeth (see subsequent section), the deciduous teeth had chronologic enamel hypoplasia. The time of disturbed enamel formation corresponded approximately with the neonatal period and the period of earliest infancy.

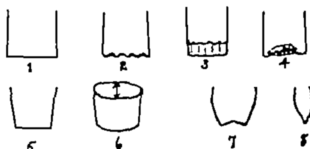
Brauer and Blackstone found that syphilis had no effect on the eruption or exfoliation of the teeth.

Morphology of the Syphilitic Upper Central Incisor.—Hutchinson's original (1861) description of the malformed permanent central incisor states that it is shorter and narrower than normal with mesial and distal sides converging from the gingival margin to the incisal edge. Failure of development of the central mamillon causes formation of a half moon shaped notch on the cutting edge. Deficient enamel covering on the incisal edge permits staining of the underlying dentin and consequently this portion of the tooth may become darkened. In 1887 Hutchinson stated that he did not believe the notching to be essential and introduced the descriptive term "screw driver" form (see Fig. 818). The upper central incisor undergoes ossification from three centers largely in the first year of infancy. During or just preceding this period, any nutritional disease or febrile illness may leave traces upon the developing tooth causing defective dentinization and enamel formation, pitting and serration. As a rule in nonspecific disturbances, the three centers develop equally however and the tooth on eruption presents the parallel or slightly flaring sides of the normal tooth. The distance between the teeth may be influenced by their general underdevelopment as well as the narrowing of the jaw so that they may appear abnormally far apart or abnormally close.

In syphilis the effect on the ossification centers of the upper central incisors seems to differ in character or time exerted from that in other diseases. The middle denticle which forms the central portion of the tooth, is suppressed and the lateral denticles, by their continued and uncompensated growth produce the bulging sides and anteroposterior thickening or "barrel shape" of the characteristic syphilitic incisor. The cutting edge of the tooth, lacking the portion produced by the middle denticle bears a crescentic notch or defect, most marked on its anterior surface. The shape of the entire tooth, rather than the notch alone is characteristic.

Figure 818 gives in condensed form the morphology of the hutchinsonian incisor and its differentiation from other types of nonspecific serration and notching.

The classical upper central incisors of heredosyphilis are shown in Figure 819 Such teeth may we think, be regarded as pathognomonic. On the other hand, the "pegging" and the widening of the spaces between the lower in-



1 Normal teeth slightly diverging sides
2 3 4- Non-syphilitic serration and etching
5- Hutchinsonian incisor converging edges (screw-driver shape)
6- The Hutchinsonian incisor is truncated cone
7- The pegged Hutchinsonian teeth
8- Sagittal section showing antero-posterior thickening

Fig 818.

cisors cannot be regarded as distinctive of *syphilis, although it often occurs* among the dental dystrophies of heredosyphilitic patients. The legends describe the differential points.



Fig. 819 —Typical hutchinsonian teeth

Sarnat and Shaw (1942) give the following important differential characteristics in the diagnosis of the hutchinsonian incisor: It is important to recall that, in congenital syphilis, the dentino-enamel junction is dwarfed. Consequently the crown is smaller This should not be confused with enamel hypoplasia (chronologic enamel aplasia) which is not in the outline of the dento-enamel junction but in the enamel formation. Hypoplasia occurs at later time and may be caused by rickets, hypoparathyroidism or fluorosis.

In partial anodontia, arachnodactylia, facial hemiatrophy mongolian idiocy achondroplasia and few other conditions, the upper permanent incisors may have narrowed dentino-enamel

junction and a peg shape. Whereas the incisal third is affected in hutchinsonian incisor the entire crown is affected in these other conditions, and the remainder of the teeth show similar



Fig. 840.—Syphilitic upper central incisors without the notching. This patient had had interstitial keratitis, undiagnosed for years, had become almost totally deaf, and had suffered collapse of the nasal septum, before syphilis was sufficiently suspected to lead to blood serologic test and treatment. Note the rounding of the anterior face of the incisor due to anteroposterior thickening, and the "screw-driver" shape.



Fig. 841.—Borderline incisors in boy with interstitial keratitis, facies, and positive blood serologic reaction. A diagnosis could not be based on such teeth, but their anteroposterior thickening and rounding of the face might stimulate further study.



Fig. 842.—Upper central incisors in heredosyphilitic patients, showing the fusiform or nut shaped tooth with bulging sides and anteroposterior thickening. Note also the pegging of the lower incisors. These teeth arouse suspicion, but are not diagnostic.

disturbances which cannot be correlated on chronologic basis with events during the neonatal period and earliest infancy. This will usually make absolute differentiation possible.

Roentgenographic Demonstration of Hutchinsonian Teeth.—The demonstration of unerupted hutchinsonian teeth radiologically was first accomplished by Stokes and Gardner in the case of a five-year-old child who had lost her



Fig 883—Traumatic notching of the upper central incisors. This patient was suspected of having heredosyphilis and the photograph has repeatedly been so diagnosed. The notching was produced when the patient face was stepped on in football scrimmage. He had tuberculous glands.



Fig. 884—A suspicious right upper central incisor markedly thickened anteroposteriorly in patient with heredosyphilis and positive blood serologic reaction.



Fig. 885.—Nonsyphilitic dental dystrophy Hutchinson, in his original description, warned against regarding this picture as due to syphilis. Painstaking investigation of this patient and her family was entirely negative. The "pegging" of the lower incisors cannot be trusted in diagnosis.

first dentition incisors and whose delayed second dentition incisors had not yet erupted. Meyer Buley from the Bonn (E. Hoffmann) Clinic has confirmed our observation, finding it usable in diagnosis as early as the second year Quinlan from Schamberg's Clinic found hutchinsonian incisors in 2 of 14

cases, Sarnat and Shaw (1942) in four of sixteen cases. The appearance should be distinctive for diagnosis

The typical notch and bulging sides are apparent in Fig 837 By having the child bite firmly down upon the film it is held in position sufficiently well for this purpose and little cooperation is required. A particular interest attaches to this case because the child's infection was recognized when she was four months old. Six injections of arsphenamine reversed the blood serologic reaction, controlled the gummatous manifestations, and reduced the infection to quiescence. When seen more than four years later the child was in excellent health and without gross



Fig. 836.—Aplasia of the upper central incisors with conical malformation of the laterals, picture occasionally seen in heredosyphilis and in congenital ectodermal defect.

evidence of syphilis, and was still seronegative. Yet the treatment which had accomplished the seemingly good result, given her at the age of four months, had failed to protect or influence the anlagen of the second dentition incisors.

The low vitality and inability to resist decay so frequently observed in the first dentition teeth of syphilitic children, may affect the second dentition teeth though much less frequently. Occasionally one finds the upper central incisors partially or completely destroyed in spite of considerable protective effort, while the remaining teeth, apart from dystrophic shape, seem



Fig 837 —Unerupted Hutchinson upper central incisors demonstrated by roentgen ray in child aged five years.



Fig 838.—The mulberry or six-year molar in heredosyphilis. Note the dwarf cusps of the anterior tooth and the hypertrophied enamel ridge which surrounds them.

quite sound. This circumstance is hardly diagnostic, however Stathers (1942) found that with the exception of the first molars, the permanent teeth seemed no more susceptible to caries than could be expected from the general dental care of the group examined.

The Mulberry Molar—The first molars of the second dentition erupt at about the sixth year and, if seen before decay sets in, present a deficient development of the cusps which is due to suppression not unlike that which

affects the middle denticle of the hutchinsonian incisor A shoulder of enamel bulges out around the crown of the molar and from well within the margin spring the four defective, dwarfed cusps (Fig. 828) deficient in enamel and usually early victims of decay Once caries sets in, the cusp is soon replaced by a pit. The cross-ribbing of the grinding surface with enamel and pitting from decay have earned it the name "honeycomb molar"

Wall and Stoll consider the mulberry molar more frequent and suggestive than the hutchinsonian incisor *If the latter term be strictly interpreted, this is probably so, but we feel more* hesitation in stressing the molar in an interpretation than we do the incisor It is, none the less, very valuable clue when typical and may be the only dental abnormality in the mouth of an undoubted, serologically positive, otherwise negative patient, with complete substantiating family history

Recent writers, particularly with the use of the roentgenogram, have stressed the importance of the mulberry molar as diagnostic sign of congenital syphilis. Stathers (1942) found that this type of tooth was or had been present in 66 per cent of his cases studied as compared with 60 per cent typical hutchinsonian teeth in the same group of patients In the forty patients in whom the first molars were still present, all four teeth were affected in 13 cases, there were 3 mulberry molars in 7 cases, 2 in twelve cases and 1 in 8 cases

The roentgenogram was first used to demonstrate the unerupted mulberry molar by Pincherle (1937). Excellent radiographic reproductions of the mulberry molar are given by Sarnat, Schour and Heupel (J A. M. A., June 21, 1941). Johnston, Anderson and McAlenney (1941) showed conclusively by direct comparison, that the mandibular first molar was smaller than the mandibular second molar in 80 per cent of their cases of congenital syphilis in which the teeth could be measured. They further emphasize the importance of the roentgenogram when they state that only one half of their 36 patients showed dental stigmata to clinical examination, whereas two thirds showed diagnostic changes in the roentgenogram.

The very obvious dystrophic tendencies of syphilitic teeth have led to multiplication of dental signs of heredosyphilis, which we think is not justified. The so-called "Carabelli tubercle, an accessory cusp on the inner aspect of the upper first molar has been supported as diagnostic point by Sabouraud. Sprawson and Dennis have examined both children and adults to the number of more than 500 without finding anything to support the claim. Our own experience has been similar

The small proportion of entirely normal teeth (30 per cent) in heredosyphilis, as shown by our series, is evident in Figure 817 The large proportion of nonspecific dystrophies is evident.

Should a diagnosis be based on teeth alone? The classical hutchinsonian tooth can be regarded as practically pathognomonic, and we have never known the finding to remain unconfirmed by history or course. The suggestive types cannot, of course be accepted without some confirmatory evidence. To that evidence we would especially admit the facies (Fig. 835) which, in combination with *suspicious teeth, we have many times seen confirmed by* the familial study or the course of the case

Bone Stigmas of Tardive Heredosyphilis.—Bone changes bulk large among the recognition marks of late heredosyphilis. In general they are the result of osteitis or overlying periostitis in the earlier months of life, which produce, respectively diffuse thickening and exostosis or roughening, especially of the shafts of the long bones. Their roentgenological interpretation appears in Chapter XVI As in acquired syphilis, the tibia and the clavicle being near the surface and frequently affected are the most used diagnostic landmarks. The frontal bosses, when exaggerated sufficiently to form Parrot's nodes (natiform or "hot cross bun" skull), have a high diagnostic value but are relatively rare. The milder grades of frontal and parietal prominence have less weight. Jeans believes many of them to be rachitic. In addition to these osseous residua, active periosteal and osteomyelitic lesions may occur in tardive cases, quite often in association with outbreaks of interstitial keratitis.

Chief among these are periostitis of the tibia and fibula, and of the radius and ulna and symmetric hydrarthrosis especially of the knee.

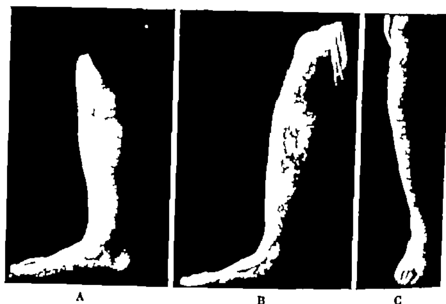


Fig. 829.—Types of saber tibia in tardive heredosyphilis.



Fig. 830.—Technic of palpating the saber tibia to detect the fusiform thickening, which is quite as important as the anterior bowing.

The older literature contains references to a nonarticular diaphyseal process adjacent to but not involving the joints and simulating tuberculosis; and arthritis leading to ankylosis the status of which with reference to syphilis is still unsettled. Bone gummas are occasionally seen Charcot joints

and spondylitis are among the rare manifestations. The frequency of these various types of lesions is indicated for our experience in Fig 810 In addition



Fig. 831.—Roentgenograms of the right tibia shown in Fig 830. The fibula also shows slight involvement.



Fig. 832.—Anterior bowing of the tibiae due to rickets. Note the absence of osteoperiosteal thickening. (Collection of Drs. Keidel and Moore.)

to the actual bone syphilids, certain developmental bone stigmas, such as the high palatine arch previously mentioned under dental abnormalities, and scaphoid scapula to be described, have a much lower diagnostic value.

The Saber Tibia.—Anterior bowing of the tibia is not sufficient of itself for a diagnosis of saber tibia. A case of rachitic origin is shown in Figure 831. The combination of bowing with thickening is essential to the full value of the sign. This thickening is usually fusiform, involving the middle third of the shaft, and palpable not only as a widening between the two fingers, as shown in Figure 830, but also as a rounding of the sharp edge and flat anteromesial face of the bone (Fig. 829). *If there has been no periostitis, there may be no roughening or pitting whatever.*

Marked grades of saber tibia are apt to be accompanied, according to Codman, by localized cortical thickening of the fibula, but this is detectable only by roentgenogram. If active periostitis is present, it differs in no respect from that described for acquired syphilis. The thickening of the tibia produced by chronic syphilitic osteitis, as seen roentgenologically, is described by Aikens as a diffuse, uniform, distended and spongy bone shadow.



Fig. 833.—A marked grade of epiphyseal enlargement in a child of seven years.

Clavicular Enlargement.—While this is not common it is often overlooked. The demonstration of gross thickening of the inner third of the clavicle with roughening and irregularity should be checked by roentgenray examination. Figure 50 is an excellent clinical illustration. Higoumenakis has stated that this enlargement tends to be unilateral, occurring on the right in right-handed and on the left in left handed individuals.

Dorne and Zakon (1933) found this sign present in all of their 14 reported cases. Yang (1940) reports the sign in all of his 6 patients with late congenital syphilis. Higoumenakis (1930) stated that it could be found in 86 per cent of cases. According to this last mentioned author the enlargement of the sternal extremity of the clavicle, as proved roentgenographically, results neither from a defect in the statics of the patient nor to a loosening and distention of the articular capsule, but merely to an augmentation in the volume of the bone caused by a hyperostosis resulting from a syphilitic osteitis. Since anatomically the inner third of the clavicle, the area involved, arises from a secondary nucleus which appears between the eighteenth and twentieth year, it would seem that occurrence of the sign might indicate activity of the congenital infection in adult life.

and further that the sign would not be present in patients adequately treated in infancy or childhood. Aldach (1941) encountered the clavicular sign in 4 of 92 patients with definite diagnosis of late congenital syphilis.

Epiphyseal Enlargement.—This is relatively frequent among bone changes in older syphilitic children appearing as a disproportionate enlargement of the joint when compared to the skeleton as a whole. The "heavy knees" and large wrists and elbows are not altogether trustworthy however and the roentgenogram may be helpful, although as a rule, no active chondro-epiphysitis remains. The shortening of the long bones, due to epiphyseal changes, may occasionally by contrast, accentuate the impression of enlarged joints. Figure 835 is an unusually pronounced case.

Osseous Overdevelopment.—We have no intention of proposing a new stigma of heredosyphilis, but it is none the less interesting to note the usual contrast between the malnourished or rachitic frame and the skeleton of the heredosyphilitic child. The tendency to bony overgrowth in the latter manifests itself in a heaviness of limb, a columnar massiveness and lack of modeling of the lower extremities which may or may not be dependent on unrecognized osteitis of the long bones in infancy

Dactylitis.—This is most diagnostic in the first year or two of infant life, but may be seen occasionally in older children, in whom a differentiation from tuberculous spina ventosa must be made. Our incidence of 2 per cent corresponds exactly to that given by Still.

The fusiform swelling of the proximal phalanx rarely softens or breaks down in syphilis as it does in tuberculosis. The finding of periosteal involvement as well as the osteochondritis of the epiphyseal end of the diaphysis, with less destruction and more thickening due to actual excess bone formation, is in favor of syphilis. The tuberculous process is usually solitary; the syphilitic and rachitic, multiple (Brickner Ware). The possibility of confusion with syphilis through false therapeutic test is illustrated by Figure 612.

Symmetric Hydrarthrosis (Clutton's Joints) —This painless hydrops, unassociated with bone changes and usually bilateral, involving the knees was fully described by Clutton in 1886 though noted earlier by Richet (1853) Förster (1877) and Virchow (1884) A synovitis is the primary and most important pathologic process. The disease is confined to syphilitic children and is the most common form of syphilitic change of the joints in the congenital variety of the disease A number of illustrative cases have come to our attention over a period of years (see Fig 596) The joint is usually not tender and shows no crepitus or other findings of note except the effusion, with consequent separation of the joint surfaces. Febrile reaction is usually absent unless from intercurrent disease or unless the joint has been aspirated for diagnostic purposes, not an infrequent procedure if the condition remains unrecognized. The roentgenogram is negative except for enlargement of the joint cavity Blood serologic test for syphilis is almost uniformly positive (Klauder and Robertson, 1934 report two seronegative cases in their series of 63 patients)

Although the knees are the usually involved joints, the condition has been reported as occurring also in the elbows, wrists, fingers and ankles. The maximum age incidence is from eight to fifteen years and cases are rarely seen prior to five years or after twenty years. There are two types (1) congestive bursitis, (2) hydrops. Gummas of the bursa may produce similar clinical picture.

The diagnosis, according to Pendergrass, Gilman and Castleton is dependent on: (1) presence of constitutional syphilis, (2) spontaneous development independent of trauma, (3) slow evolu-

tion and chronicity (4) absence of pain, tenderness or functional disability (5) symmetrical involvement usually of the knees without evidence of bone involvement, (6) response to specific treatment.

Klauder and Robertson (1934) state that, untreated, the condition may exist for months or even years but tends to terminate with spontaneous recovery. Treatment for syphilis probably shortens the course of the disease but improvement (in the congenital form in contradistinction to the acquired form) is seldom rapid. When the effusion disappears, the joint becomes normal,



Fig. 634 —Osteoperiostitis of the ulna in heredosyphilis. The child had every stigma of the disease except venous ectasia.

relapse seldom occurs, ankylosis is not a feature and surgical intervention is normally unnecessary and contraindicated.

The so-called "von Gies joint," in contradistinction to Clutton's joint is a syphilitic chondro-osteo-arthritis which may lead to ankylosis. Fournier describes a polyarthritis with changes resembling arthritis deformans which is probably closely related, if not identical with, von Gies polyarthritis. It occurs in older children and is decidedly rare.

Since interstitial keratitis is the commonest active clinical manifestation of late congenital syphilis it is not surprising that it is frequently associated with Clutton's joint. Instances are not

uncommon in which treatment of one of these conditions seems to have precipitated the other. Klauder and Robertson (1931) found that Clutton joints were slightly more common in patients with interstitial keratitis than with other manifestations of congenital syphilis but review of the literature and of our own experience fails to indicate that, from the statistical standpoint, there is any apparent relationship. Of some practical importance is the fact that at times Clutton joints precede the development of interstitial keratitis chronologically in the course of development of the disease and, if recognized, may form valuable premonitory sign to the more serious eye involvement.

Developmental Stigmas and Constitutional Inferiorities.—The developmental stigmas not already considered include disturbance of the age-development ratio, constitutional inferiority giantism and infantilism, venous ectasia, general hypertrichosis, the bony abnormalities of cranial bosses,



Fig. 633.—The classical "map of heredosyphilis, with all accessories, including bosses, corneal nebula, and hutchinson incisors. Examination failed to reveal any evidence that this patient had ever had osteitis of the nasal septum to account for the flattened bridge.

scapulae, palate and middle fingers, and that most interesting and significant of composites, the facies. There is little of specific value in the majority of these items. Venous ectasia is most apparent in the enlargement and tortuosity of the superficial scalp veins. A retiform blue tracery may be rather conspicuous over the upper thorax, and the external jugulars may seem unusually large and corded. The anomaly is, however frequently absent or becomes inconspicuous as the child grows older The chief disturbances of age-development relations concern late walking, which is not especially characteristic of the syphilitic child over or underdevelopment amounting at times to dwarfism or giantism, and delayed puberty especially in girls. The eccentric development of the syphilitic child seems not to be especially distinctive in any particular unless it be the mental side discussed on page 1145 For a period of several years the Section of Dermatology and Syphilology at the Mayo

Clinic made numerous examinations of constitutionally inferior children in the effort to trace syphilitic dystrophies, with very disappointing results. While the child with a severe syphilis may for a period exhibit a good deal of depression the large majority of tardive types are not as ill or underdeveloped as the seriousness of the disease would lead one to expect. DeAngelis reached the conclusion that most of the undernutrition of the child was due to environment, not the disease. They are in a sense a picked group, who have survived the grueling test of uterine and infantile infection and not infrequently include very fine specimens of athletic young manhood and attractive girlhood. Even the sharply stigmatized patients have little of a general nature to complain of. The impressions conveyed by the monstrous exhibits of the visitation of the sins of fathers on children do the heredosyphilitic child the grossest injustice. Of grossly crippling deformity and disfigurement there is very little indeed.

Endocrinopathies as a Source of Stigmas.—Opinion on the influence of syphilis upon the endocrine mechanism controlling growth in the heredosyphilitic child continues in the speculative stage. The demonstration of syphilitic lesions or spirochetes in such organs as the suprarenal glands and testes does not necessarily imply structural or functional change. That there are endocrine changes in syphilis, however, is evident from the studies of Brown on the rabbit. The French and Italian writers in particular are inclined to attribute a variety of dystrophic changes to the influence of syphilis upon the endocrine mechanism. In the case of pituitary dystrophies the connection is more apparent than following many of the thyroid and gonad disturbances for which a causal relation is claimed. Progeria, that astonishing picture of senility in childhood described by Gilford and more recently by Curtin and Kotzen, whose case we saw, compares for example with Simmonds' disease in which acquired syphilis of the hypophysis is implicated. Progeria, however, is not prenatal syphilis so far as is now known. Syphilis seems, at times, also to impart a species of developmental stimulus to the organism, expressing itself in hypertrophies of structure and vivacity, of which the precocity and physique of well-developed syphilitic children are examples. Very little that is tangible and diagnostically useful, however, can be derived from this material at the present time. For more recent discussion of this subject in relation to the pituitary and thyroid see Bleus (1938, 1939).

The Facies of Heredosyphilis.—The facial make-up of the heredosyphilitic child in a typical case is a composite of syphilids and developmental dystrophies. The rhagades, the dimming of the eyes from corneal nebula, the flattening of the nasal bridge through collapse of the nose following gummatous osteitis of the septum, the hutchinson incisors, create an impression sufficiently obvious for detection by the tyro. There is, however, a special and more occult "impression" produced by the facial make-up of heredosyphilis, which is independent of these grosser stigmas, and which rests apparently upon anomalies in embryonic development similar perhaps to those which produce the grosser teratologic monstrosities of oxycephaly, acrocephaly, turricephaly, and acrocephalosyndactylism, and the dermatological rarity of congenital ectodermal defect.

The difference between the normal and the heredosyphilitic face does not depend on any one feature, but resides mainly in the upper part above the upper lip and at times even above the tip of the nose. A certain touch of fulness and excess breadth and height to the forehead is an element, yet the rachitic and constitutional inferiority complexes may have it without giving the true impression. False impressions may be had by relying too much on the beetling or Olympic front. The essence of the matter lies in a certain maleficness, a sleepy, tired, fagged, clouded, dreamy or obscured appearance of the upper face, an appearance of veiledness as if a smudge had lightly swept across



Fig. 836.—A, The facies of heredosyphilis. The suggestion of apathy, listlessness, fatigue, and "blurring" or "smudging" is not produced by focusing defects, for with a hand lens the lanugo hair between the brows and the delicate cleavage lines of the skin can be recognized in the original photograph. The boy had never had interstitial keratitis. The blood serologic test was positive. He had double dacryocystitis, which was practically quiescent when the photograph was taken. The "facies" is not lost by distortion of the lower face, nor is the forehead essential. In B the forehead is covered, there are no upper central incisors, and the "grin" showing the lower teeth does not conceal the impression.



Fig. 837.—A less pronounced, but nevertheless definite facies, estimated at 60 per cent. Note the look of fatigue and apathy, though the patient was well. She had a right upper central incisor quite definitely of the syphilitic type, a negative blood serologic test, saber shins, and interstitial keratitis. Her mother had a neurosyphilis of long standing.

the brows and eyes and the nasal bridge of a crayon portrait. It is possible to obscure the jaw and mouth with a card and still get the impression. Changes in expression (Figs. 836, 837) and angle of inspection do not destroy it. Wile

has laid stress upon the upward and outward flare of the nostrils which results from the depression of the nasal bridge and this is undoubtedly important. To us, however the effect is produced more by the increased distance between the eyes. Neither corneal nebula nor teeth are essential. With the brows more accentuated and the eyes deepened, with the blue iris and black pupil in sharp contrast, the facies becomes Celtic. We have seen the "map of Ireland in a deaf girl produce a quandary among experts.

The impression or facies of heredosyphilis may be sufficiently clear cut to permit the expert to make diagnosis with an accuracy exceeding 90 per cent, and it may prove just the reverse The conversion of the "impression into words is difficult, and reinterpretation should be undertaken only with photographs and the patient before one. Mere verbal description is not a safe basis for diagnosis, and only experience gives actual assurance. The chief value of the facies is in the arousing of suspicion, which should then seek confirmatory clues, for the facies should practically never be allowed to make the diagnosis alone.



Fig 838.—Brother and sister each with certain of the elements of the heredosyphilitic facies. The dome in the boy case is less suggestive than the face of the girl. There is corneal nebula of the right eye which heightens the effect.

Familial resemblance and subjective interpretation must be watched in passing an opinion upon the facies. *Two or three observers* should, if possible, form independent opinions before comparing notes. The actual diagnostic value of an expert ppraisal of this clue is difficult to state, but it certainly greatly exceeds in value such items as scaphoid scapula, high palatine arch and the numerous minor and debatable signs. In fact, we would place it among the major diagnostic aids, never acceptable alone, but of great confirmatory value.

The differentiation of the heredosyphilitic facies from other types is not difficult. A box shaped head and square beetling forehead is rachitic rather than syphilitic and if nothing else can be found cannot be trusted as a sign. The open mouth and vacant look of the adenoid type emphasize the lower face. Constitutional inferiority and idiocy are caricatures, which the facies is not. The long keystone or horse face is emphasized by some writers. Mongols have the slit eye, the overlapping inner canthus, the high cheek bones, and macroglossia to distinguish them In progeria the caricature of senility—huge dome (suggesting hydrocephalus) wasted ears beaked nose, and underdeveloped

jaw and clavicles, with the skeletal underdevelopment, sexual retardation and atrophic skin are distinctive.

Frontal Bosses.—The minor degrees of frontal prominence and even quite pronounced bosses cannot be regarded in spite of their frequency as



Fig. 839.—A family group illustrating mild grade of oxycephaly The length of the face and the ears "on the neck" are better seen in profile but the absence of supra-orbital ridges and wide separation of the eyes, with the familial resemblances, are apparent.

more than contributory evidence (Fig 841) Extreme degrees, involving both frontal and parietal bones, with the anterior fontanel lying in the cruciate depression between them, are however considered as almost pathognomonic.



Fig. 840.—The facies of congenital ectodermal defect. The patient had neither hair (wig) nor sweat glands and few teeth. Note the flattened nasal bridge. There was no osteitis or destruction of the septum.

Scaphoid Scapula.—Concavity of the vertebral border of the scapula was described by Graves (Fig. 842) as developmental anomaly which occurs in constitutional inferiority complexes, syphilis among them, without being pathognomonic of any particular condition. Wile and Mundt (1942) in their series of 402 cases found scaphoid scapula to be present as diagnostic criterion in 27 per cent.

Ulnar Deviation of the Middle Fingers.—This is an inconclusive clue found in small percentage of cases (Fig. 843).

Post-rhagadic Scars.—These lesions are in reality produced by atrophy of the elastic tissue, resulting from diffuse syphilitic infiltration of the skin such as is seen only in the congenital type of infection (see Figs. 800, 801). The lips, chin, cheek, corners of the eye or nose or perianal region



Fig 841.—Profile of the dome. This abnormality alone does not constitute a "facies.



Fig. 842.—The typical scaphoid scapula—concavity of the vertebral border of the scapula (Graves' scapula). The patient must relax to permit the slipping of the fingers under the edge as shown.

may be involved. Post-rhagadic scars of congenital syphilis on the face are distinguished by diminution in the color of the lip, by partial loss of the mucocutaneous border and by the presence of linear furrows of the lip which extend but radial scarlike lesions of the surrounding skin

(Hochsinger, 1896) Strakosch and Nelson (1941) illustrate one case with rhagades in retiform arrangement on the cheeks. Krantz (1941) feels that when the scars project as white pegs into the vermilion border or when they extend far into the surrounding skin they are pathognomonic even when other stigmas are lacking

DuBois Little Finger Sign.—In 1866, DuBois described a sign which he felt occurred in as high as 80 per cent of cases of congenital syphilis. According to DuBois the skin fold between the *terminal and middle phalanx of the little finger, is not at the level of the skin fold between the* basal and middle phalanx of the fourth finger as normally but somewhat more proximal. This sign is supposed to result from a dystrophy of the middle phalanx of the small finger. Our ex



Fig. 843.—Ulnar deviation of the middle fingers, a relatively unimportant sign.

perience has been that this is a relatively uncommon finding. Aldach (1941) has pointed out that it occurs in about 7 per cent of apparently normal persons.

Late Visceral Changes.—In spite of the supersaturation of the patient with organisms before birth, the early involvement of the spleen and liver in a large proportion of cases, the fibrosis that affects to a greater or lesser extent the pancreas and the ductless glands, and the enormous numbers of spirochetes which are demonstrable in such tissues as the myocardium, the *tardive heredosyphilitic patient presents very little in the way of cardinal* symptoms from the visceral and vascular structures. He has, in fact, conquered or subdued his infection, and survived the fibrosis which it has induced. The liver and spleen are enlarged in only a slightly larger proportion of cases than in late acquired syphilis. One of us (Stokes) has seen only three really huge spleens, one in association with hepatic cirrhosis and multiple bone lesions. The stomach and intestine have more than the relative immunity of acquired syphilis.

D'Aunoy and Pearson (1939) report an incidence of 1.5 per cent intestinal lesions in 500 children with congenital syphilis who came to autopsy. More than 75 per cent of all cases of syphilis of the intestine are observed in macerated stillborn infants and in infants who live less than twenty-four hours (see previous section on pathologic changes in the syphilitic fetus)

Cardiovascular Involvement in Congenital Syphilis.—Curiously enough, the cardiovascular system of prenatally syphilitic individuals, while demonstrably especially so far as the heart muscle is concerned, the lurking ground of innumerable *Spirochaeta pallida* in early life, presents an almost complete immunity to serious syphilitic cardiovascular disease. In his entire experience

Stokes can recall only once having seen the clinical homologue of syphilitic aortitis in child. Yampolsky and Powel (1942) have reported such a case in nine-year-old Negro girl at autopsy and have reviewed the literature in the field. They emphasize the reports of previous authors as to the likelihood of sudden death from the involvement of the mouths of the coronary arteries. Hinrichsen (1943) review points out: (1) it is often difficult in adult life, and often even in childhood, to differentiate between the congenital and the acquired form of the disease; (2) other conditions, such as acut infection, especially rheumatic fever and congenital malformations of the heart may produce aortitis and aneurysm, so that syphilis, even if present is not necessarily the causal factor (3) rheumatic fever moreover especially in its acute phases may occasionally be responsible for biologically false positive serologic tests (Koons and Kimana, 1940, Fordyce, 1930) The clinical importance and interest of the question of cardiovascular syphilis in childhood led to the presentation of three important papers before the American Heart Association in 1930, dealing with thorough studies by Previtali, Nicolson, and Moon-Adams (30 cases) clinical,



Fig. 844.—Hypertrichosis as sign in heredosyphilis. This was a girl of eleven years, with numerous other and more significant stigmas.

electrocardiographic, and roentgenological findings Givan (417 cases, thirteen months to forty-two years) and McCulloch (830 cases under fifteen years). In Givan series only 1 case with findings that might be classified as cardiac disease due to congenital syphilis appeared. All three groups of cases led their investigators to the same conclusion—that hile syphilitic heart disease occasionally ppears as reportable rarity in the literature which they review it is all but negligible in clinical practice despite the recognized occurrence of the organism in the heart muscle. The criteria for the recognition of the occasional case differ in no particular from those applicable to cardiovascular disease in acquired syphilis.

Peripheral vascular lesions, including symmetric gangrene are occasionally reported, the literature to 1914 being summarized by Lisser and Hand and Reilly having recently reported 3 children aged two and half, five and eight and half years in one family whose parents had syphilis. Of this condition Stokes has seen one case through the courtesy of Dr J C Gittings, lesion of which is illustrated in Fig. 710 Chapter XIX.

Hinrichsen (1943) has completely reviewed the literature of this subject and comes to the

conclusion that congenital syphilis produces definite myocardial lesions of two types, namely interstitial and nodular myocarditis, in which *Spirochaeta pallida* can be demonstrated. No conclusive evidence that congenital syphilis produces valvular heart lesions appears in the literature. The rôle of this disease in producing aortitis and aneurysm and in the production of congenital malformations of the heart has not been determined definitely. Arteritis, particularly of the cerebral vessels, may be produced by congenital syphilis. It is possible that congenital syphilis may be a factor in some cases in producing arteriosclerosis and Raynaud's disease. Congenital syphilis is one of the causes of hemorrhagic disease of the newborn.

The above statements should not leave the impression that the heart of the congenital syphilitic to ordinary physical examination is a normal-sounding, normally functioning heart. A number of minor abnormalities—split second sounds, tachycardias, over-action etc.—suggest the contrary, though no specific pathologic abnormality may be recognizable.

Neurosyphilis and Nervous Disorders in Tardive Prenatal Syphilis.—The importance of this group of manifestations is evident from the place of neurosyphilis (26 per cent) mental retardation (25 per cent) nervousness (22 per cent) and precocity (12 per cent) in our table of signs (Fig 810)

Neurosyphilis presents the same forms in the tardive heredosyphilitic that it does in the adult, but with some recognizable differences in symptomatology especially in tabes. Paresis, tabes, and taboparesis, cerebral arteritis, meningitis and meningo-encephalitis, spastic diplegia, epilepsy and imbecility are all recognized as occurring in heredosyphilis. There is also an asymptomatic type which could undoubtedly be recognized earlier and effectively treated if more attention were paid to the spinal fluid examination in the young child.

The 92 cases of tardive congenital neurosyphilis recently reported by Wile and Mundt (1942) were analyzed into 46 per cent asymptomatic, 21 per cent paresis, 11 per cent tabes dorsalis, 3 per cent taboparesis, 3 per cent meningovascular 2 per cent meningitis, 1 per cent cranial nerve palsies. A miscellaneous 10 per cent was composed of patients with epilepsy convulsive disorders, hydrocephalus and mental retardation.

Unrecognized Juvenile Preparesis.—The medical profession has not appreciated its responsibility in identifying neurosyphilis in children and young adults by spinal fluid examination at the earliest possible moment after syphilis is recognized. The Army Selective Service and inductee examinations are disclosing the frequency of such shortcomings. After months and years of routine ineffectual treatment for an irreversible serologic test in a child or adolescent, a spinal fluid examination after a "nervous breakdown" or a selectee or employment serologic test discloses the existence of a paretic formula. The then grave clinical situation and impending tragedy could have been averted by fever therapy at least had the practitioner in the case recognized the necessity A spinal fluid examination early in the course of congenital (prenatal) syphilis is as essential as in any phase of acquired syphilis.

The analysis of our cross section of 150 patients completely examined with reference to the nervous system showed that 20 per cent had abnormal spinal fluids (Figs. 845) and 20 per cent had some form of neurosyphilis. The proportion is greater the younger the patients in the group, ranging from 31 per cent between the ages of birth to nine years and 17 per cent between ten and nineteen to 10 per cent in the third decade and none at all over thirty

These figures correspond closely with those of Jeans and Cooke (1930) and Wile and Mundt (1942). Jeans found that 40 per cent of his syphilitic infants, 31 per cent of older children with active lesions, and 20 per cent of older latent cases showed involvement of the nervous system. Wile and Mundt found positive spinal fluids in 47 per cent of their cases under two years and in

27 per cent of their cases over two years. In each type of clinical congenital neurosyphilis males were affected more frequently than females in the ratio of three t two. The tendency of neurosyphilis toward a fatal ending in infancy or early childhood probably accounts for some of the decline in the older age groups. It may moreover serve t explain the differences noted in various reports. Figure 845 summarizes several of the recent estimates in the literature

Meningitis.—Meningitic symptoms appear most frequently in the younger children—40 per cent of Jeans and Cooke s children under one year of age. The symptoms are not distinctive Kernig sign neck rigidity and an onset with convulsions. In half their cases there was a bulging of the fontanel. The serological tests are positive the cell counts high often 500 or over Treatment response is good.

Hydrocephalus. Congenital syphilis is frequently the cause of hydrocephalus internus of moderate degree but involvement is seldom so marked as t cause hydrocephaly of the dimensions

Fig. 845.

INCIDENCE OF NEUROSYPHILIS IN HEREDOSYPHILIS

Author	*Date*	*Cases.*	*Spinal fluid abnormal per cent.*	*Clinical neuro-syphilis, per cent.*	*Remarks.*
Jeans	1919	214	32 7		None over fourteen years.
Taeuser	1921	45	41 8		
Kingery	1921	58	28 8		
White and Veeder	1922	206	30 6	17 8	Infants.
Stokes	1924	150	20	10	33 per cent over fourteen years.
Jeans and Cooke	1930	137	38 7	8 8	White under two years.
		140	22 9	4 3	Negro under two years.
		249	29 7	10 5	White over two years.
		190	12 5	1 7	Negro over two years.
Menninger	1936	653		less than 10	43 cases of author 610 cases collected from literature
Wile and Mundt	1942	19	47	36	Under two years.
		843	27	11	Over two years.

sometimes reached result of congenital malformations (Benda and Tedgell, 1941). Woodall (1929) found prevalence of syphilis of 11 1 per cent in hydrocephaly and 7 1 per cent in microcephaly. Hydrocephalus appeared in 30 per cent of Jeans and Cooke group of children with neurosyphilis. The cell count on the fluid is increased but not as high as in the acute meningitis. With early and adequate treatment these authors found the response to be good.

Juvenile General Paralysis.—The onset of juvenile general paralysis may be veiled by the youth of the patient, and lacks the striking features of the adult type in part because of the psychically undeveloped nature of its victims. Menninger found that juvenile paresis represents less than 2 per cent of all cases of general paresis, and between 5 and 15 per cent of congenital neurosyphilis. Less than 1 per cent of all cases of congenital syphilis develop paresis. The average age of onset is thirteen years, 68 per cent of cases being between nine and eighteen years, with 0 4 per cent becoming manifest before

W. C. Menninger s excellent monograph entitled Juvenile Paresis, Baltimore Williams and Wilkins Co., 1936, should be read by all interested in detailed study of this subject.

the age of six years and 3 6 per cent after the age of twenty Epileptiform seizures, mild grades of conduct disorder and imbecility are the presenting symptomatic aspects in most cases. Not infrequently before the onset the child may present a normal or even a precocious mentality Failure to pass a grade in school may be the first warning, and months and even years of slowly progressive retardation may only finally be unravelled as the dementia becomes complete, by an examination of the spinal fluid.

Gardner (1930) reports accurate measurement of physical and mental growth in patient with juvenile paresis, over period of years, both before and after the appearance of clinical symptoms. Both mental and physical development were normal up to the age of ten years when he suddenly failed to progress in school. With the development of symptomatic paresis physical growth ceased over period of five years and learning capacity fell to the imbecile level. Antisyphilitic treatment was more effective in reinstituting normal physical growth, than it was in restoring normal mentality

Menninger (1936) concludes that the mental symptomatology of juvenile paresis is characterized by confusion, mental regression to simple dementia, inadequate emotional response and restlessness. Clinical pictures approximating psychoses of the adult are infrequent, because of, as is pointed out above, the undeveloped nature of its victims.

It is often not easy adequately to differentiate the mental symptoms produced by congenital neurosyphilis from those produced by heredity and environment. Menninger reports that mental disease (exclusive of dementia paralytica) sufficiently severe to require hospitalization occurred in one or more nonsyphilitic members of the family in 14 per cent of 399 cases. Jenkins and Crodela (1941) in study of the relation of juvenile paresis to behavior problems in children state that the paresis contributes largely to such traits as restlessness, exclusion from school, poor work in school, distractibility emotional instability excitability immaturity and childish manner and destructiveness; and that traits referable to such factors as lying, stealing, truancy and sex delinquency though frequently associated with paresis, are the result of environmental and parental influence rather than of disease.

Klauder and Solomon, who have reviewed this subject with presentation of 23 cases, found the age onset of symptoms to lie between six and fifteen years, lapse of time from birth corresponding quite clearly with that observed in adults. They comment on the recurrent convulsive or epileptiform seizures which may occur daily for long periods of time with strikingly little effect on the patient. Toni Schmidt Kraepelin, with series of 64 cases, found one fourth of their patients showing arrested development, one third with mental deficiency The studies of Howard (1936), Jenkins, Brown and Cisler (1940) and of Lurie, Greenebaum and Brandes (1941) all show that syphilitic children with involvement of the nervous system tend to be intellectually inferior to their nonsyphilitic siblings and to groups of children in the same economic strata. The latter authors found that by the Stanford revision of the Binet test only 29 per cent were of verage or superior intelligence, whereas 60 per cent ere distinctly below normal. The epileptiform symptoms with focal signs suggest brain syphilis in some cases, and in others, to judge from Dahlstrom cases, may suggest brain tumor and lead to needless surgery especially in those not infrequent cases in which head injury precipitates.

The most important single group is, of course the preparetic, recognized by all the writers cited, in which a typically paretic spinal fluid unaccompanied by symptoms occurs. The improved outlook for paresis under modern treat ment makes it doubly important to seek early identification of these cases by spinal fluid examination.

The clinical stigmas of prenatal syphilis may or may not be present in patients with juvenile paresis. As a rule, in our experience, those who present marked stigmas seem to suffer from a more severe infection, and to have undergone an earlier and more pronounced degeneration. The discovery of a juvenile paretic in a family should be a signal for examination of parents and other children.

In Frühbeck series 16 per cent of the parents had paresis, and an additional 13 per cent had other forms of neurosyphilis (quoted by Klauder and Solomon) Kemp and Poole found neuro-

syphilis eight times as frequent in mothers and three times as frequent in fathers of twenty families with neurosyphilitic children as in twenty normal controls. Jeans and Cooke wisely emphasize that not all mental deterioration in prenatal syphilis is paresis, and much that passes as paresis may be meningovascular syphilis, which is common in syphilitic children.

Juvenile Tabes.—The juvenile tabetic runs a milder course than the acquired type. It is rare indeed to see the pronounced ataxias and the severe subjective symptoms of the adult. The taboparetic type is not uncommon, the proportion of this type to the whole being swelled perhaps, by the undoubted cases of early arrest with minor and unrecognized neurological signs which escape detection of which we have seen several excellent examples. The insignificance of symptoms in the tabetic child makes these signs the more easily overlooked.

Parker who reviewed number of the cases seen at the Mayo Clinic, directed attention to the large immobile irregular pupil in contrast with the myosis of the adult type and the frequency of optic atrophy and urinary incontinence. The latter is marked enough to justify a thought in children who have late enuresis. Both Rosenbeck and Parker found the average age onset to be fifteen years. The *former found* blindness from optic atrophy in 40 per cent of his cases. Parker noted 3 cases with neurological signs, but negative fluids in his series. White and Veeder (1921) found a 12.6 per cent incidence of optic atrophy in 79 congenital neurosyphilitics and Lemaresse and Jeans (1937) an incidence of 22 per cent in 19 cases. The early treatment of congenital syphilis decreases directly the incidence of neurosyphilis and consequently of optic atrophy. Tabetic gastric crises with negative spinal fluid can occur in the child, and offer possibilities of confusion with the cyclic vomiting associated with septic foci. They are as resistant to treatment in the cases e have seen as are the crises of adults. Rosenbeck states that trophic disturbances do not occur but Stokes has seen Charcot spine in a juvenile tabetic.

Cerebral Arteritis.—Hemiplegia of syphilitic origin may develop in syphilitic children An early symptom may be obstinate and intractable headache terminating suddenly in a vascular accident or epileptiform convulsion. Such cases are in our experience more often unearthed in the familial examination and are apt to be seronegative on both blood and spinal fluid when seen in later life, though presenting definite physical stigmas.

Figure 883 (mulberry molars) was an example of such a case. In another instance, the father while under treatment for rapidly progressive syphilitic meningomyelitis, received word that his six-months-old daughter had just had "stroke. The child was serologically negative on both blood and spinal fluid, and the mother likewise negative on the blood, but the vascular accident lacking other apparent cause as considered justification for treatment and observation. Park and Veeder had 9 cases of hemiplegia, 4 with positiv spinal fluids, making this the second in frequency of the neurological conditions they enumerat (excepting mental retardation). In two of their cases gangrene of the leg or foot on the affected side had occurred. Additional cases have been reported by Marquézy Jammet and Chevalier (1930), Saal (1931), Mikulowski (193 Lüdtke (1933)

Epilepsy —In our experience, epilepsy at all approaching the essential type, is negligible in the clinical picture of heredosyphilis. Not a single case appeared among our 200 patients, and only 1 case in Park and Veeder's series of 443 children

Menninger and Menninger (1931) collected 51 cases of epilepsy of the so-called idiopathic type due to congenital syphilis. They concluded that congenital syphilis can produce convulsions directly and indirectly without the presence of gross brain lesions or juvenile paresis and that it *may rarely parade as idiopathic epilepsy* Whitehman (1940) concludes that it is by no means certain that syphilis can produce typical epilepsy since convulsions may occur in individuals with and without syphilis and syphilis can be present with and without convulsions. The treatment of typical epilepsy by antisyphilitic therapy even when syphilis is present has been disappointing

Baboneix (1929) reports that in study of 323 cases of essential epilepsy 54 (17 per cent) had syphilis, but in only one case did treatment result in cure of the epilepsy with some improvement in 3 additional cases. While the older literature (Solomon, Jeans) reports as high as 20 per cent congenital syphilis in epileptics, more recent studies indicate much lower prevalence. Pigott, Weingrow and Fitch (1939) report prevalence of 0.7 per cent congenital syphilis among 1,000 juvenile cases confined to the New Jersey State Village for epileptics. Baballan (1939) reports case treated for several years as idiopathic epilepsy before he subsequently developed interstitial keratitis when the family history of syphilis was first noted. Epileptic seizures, usually idiopathic and *petit mal* in type, may follow serologic involution and favorable clinical progress of juvenile paresis after treatment has been suspended.

Spastic Diplegia and Quadriplegia.—This condition seems to be quite generally accepted as a manifestation of neurosyphilis of the spinal cord in syphilitic children, but it is comparatively rare.

T cases appeared in our series and 4 in that of White and Veeder an incidence of 1 per cent. The onset is apt to be noted at the time the child begins to walk. Jeans and Cooke saw 14 cases. Mingazzini reports group reproducing the picture of familial spastic paralysis. Woodall (1929) found prevalence of 3 per cent syphilis in institutionalized cases of spastic paralyses.

Mental Deficiency—The recent studies of Benda and Tadgell (1942) have tended to confirm the older work of the Solomons which indicated that syphilis is present in about 6 to 7 per cent of the feebleminded population. They further state that from 40 to 50 per cent of the feebleminded individuals with congenital syphilis have their mental deterioration because of this disease.

Menninger (1930) approached this problem from two angles in his review of the literature (1) with respect to the incidence of feeblemindedness among congenitally syphilitic persons and (2) with respect to the incidence of syphilis among mentally defective persons. With respect to the former he found that in nine studies in the literature from 7 per cent of 148 cases to 37.2 per cent of 42 cases (mean 22.3 per cent) of congenital neurosyphilitics are feebleminded. The percentages of syphilis among mental defectives in eight studies ranged from 1.5 per cent to 8.5 per cent with a median of 4.8 and mean of 4.6.

There is definite evidence that much of the low grade mentality among congenital syphilitics is not the direct result of the disease but rather of other hereditary factors. Dayton (1923, 1930) as result of extensive statistical analysis involving some 40,000 syphilitic and nonsyphilitic, mentally defective and normal persons concluded that syphilis is negligible factor as cause of mental deficiency

Myerson (1930) points out that tremendous amount of low grade mentality and feeblemindedness occurs among the parents of the syphilitic feebleminded. While it cannot be denied that syphilis causes alterations of the brain, there is very little in the general appearance and the *reactions of the congenital syphilitic feebleminded to distinguish them from the mass of feebleminded.* Benda (1940) on the other hand, has presented histologic evidence that the pathologic process underlying feeblemindedness in some congenital syphilitics may be the end stages of meningo-encephalitis syphilitica or Nissl-Alzheimer endarteritis, and that occasionally these pathologic processes may be present in typical form at autopsy even with negative blood serologic test and negative spinal fluid study

In the large percentage of morons no signs of neurosyphilis are present, and family studies reveal the presence of hereditary factors in most instances. Congenitally syphilitic imbeciles and idiots, on the other hand, give evidence of neurosyphilis in the majority and there is every indication that, in these cases, the mental deficiency is the result of the destructive process of neurosyphilis. The material of Benda and Tadgell (1942) has shown that in study of the parents of syphilitic idiots, there was little evidence of mental deficiency in the family With morons and low grade imbeciles, however there was definite factor of heredity

It should be noted that according to some reports Mongolian idiots will frequently show biologically false positive spinal fluid-blood serologic test for syphilis and mild zone colloidal gold curve This was reported by Paddle (1933), who mentions also the work of Stephens and of Riddel and Stewart. Mongolism, is, none the less, not to be considered manifestation of congenital syphilis.

Backwardness and Mental Retardation.—A depression of the level of mental activity and energy seems to be quite frequent in heredosyphilitic children, and fortunately responds well to treatment. The importance of mental retardation as an initial symptom of serious neurosyphilis is so considerable that a spinal fluid examination is indicated in all cases in which it is at all pronounced or progressive even though the test may not be routinely performed.

White and Veeder, in 443 cases, found 18.7 per cent of mental retardation including all grades from idiocy upward, the milder grades being much the more common. In our series 11 per cent were below par mentally as expressed by slow progress in school and difficulties in adaptation, some of which is undoubtedly due to the influence of physical defect such as impaired vision, poor hearing, and susceptibility to illness causing absence from school. The studies of Luria, Greenebaum and Brandes (1931) and of Jenkins, Brown and Cisler (1940) previously mentioned show that the general tendency is for the congenital neurosyphilitic to be intellectually inferior.

Conduct Disorder.—As distinguished from mere dulness, on the one hand and active mental disturbance or juvenile paresis, on the other there is in the heredosyphilitic group a distinct type of unruly or "wild" child, difficult to manage and at times distinctly inclined toward outright delinquency. The first outright expression may be at school.

The studies of Jenkins and Cradein (1941) show that the behavior pattern of stealing, lying, truancy, sex delinquency, unconventionalism, etc. found in some juvenile paretics is the result of social and environmental factors rather than of the disease syphilis.

Precocity.—Twelve per cent of our heredosyphilitic children showed a mental development well beyond their years. In many cases in spite of the handicaps of eye trouble and susceptibility to other illness, it was quite sufficient to place them well beyond the average in school. The resemblance to the precocity of rickets and the momentarily suggestive appearance of the rachitic child are sufficiently confusing so that little reliance can be placed upon the symptom in diagnosis. It will be remembered that with any normal group of children a large percentage will be distinctly above average and an equally large number below the mean intelligence of the group. Where the mind has not been affected by the disease, therefore, precocity may normally be present in a small percentage of cases and this should not necessarily preclude the diagnosis of congenital neurosyphilis.

Nervousness.—A heightened nervous irritability is present in too large a proportion of syphilitic children to be merely a coincidence (22 per cent in our series). It may manifest itself in emotional instability, fits of temper, night terrors, the easy development of tics and habit spasms, and definite hysteric manifestations, or simply assume the form of spoiled precocity and wilfulness. The improvement which occurs under treatment is the best confirmation of the connection. The nervous make-up may appear in the children of neurosyphilitic parents without clinical evidence of the disease or with only a suggestive sign or two leaving the physician indefinitely in doubt as to the exact state of affairs and the advisability of treatment. In general we have been more inclined to demand positively confirmatory clinical or laboratory signs than to make the nervous state alone a reason for specific treatment.

Psychoses.—Nonne in particular has voiced the impression that dementia praecox is more frequent in the children of syphilitic parents than in those of

ordinary parentage. Solomon, speaking from the psychiatric standpoint, is unwilling to concede a necessary connection.

Miscellaneous Considerations. Trauma and Influence of Other Diseases. —In these matters prenatal syphilis follows the general rules applicable to the disease as a whole.

A blow on the head may precipitate the early symptoms of paresis as in two of Klauder and Solomon cases, or syphilitic epilepsy as in that of Menasse. The strain of war may bring on breakdown as in the 8 cases reported by Spackman. Bone gummas, especially of the tibia, may come on following trauma. A good example of traumatic excitation of osteo-arthritis is given in Chapter XVI. Wetting, chilling, slips, and strains are often the starting points of hydrarthroses. Deafness likewise comes on after falls. Infections may alter the course of favorably progressing paresis and bring on convulsive seizures even in older children, with permanent impairment. The precipitation of interstitial keratitis by influenza, tonsillitis, and childbirth has been mentioned. Hunt states that scarlet fever measles, and influenza are especially likely to be followed by lighting up of latent heredosyphilis.

Cyclic Vomiting.—The entire question of syphilis as a factor in cyclic vomiting of childhood needs thorough revision in the light of focal infection, acetonemia, etc.

In two cases under Stokes' observation treatment was apparently effective in one, but while the boy had positive blood serologic reaction repeatedly little could be found to support it in the family. A year later he had another attack associated with a typical toxic erythema and diarrhea. The beneficial effect of treatment was possibly that of intestinal antisepsis, and perhaps nonspecific action on streptococcal focus. In the second case the girl, fifteen years of age, had vomited for several days at intervals ranging from month to six weeks. The only evidence of syphilis in the entire family was her repeatedly positive blood serologic reaction. This and the vomiting were alike uninfluenced by treatment, and finally in perplexity the patient was sent to two other serologists for examination, both of whom returned unqualified negatives with several antigens. The mechanism of our repeated and probably biologically false positive result remains obscure. Ingraham (1935) mentions one case in his series which was operated upon for partial pyloric obstruction. Continental writers such as Vaglio report 75 per cent of syphilitic origin in 20 cases. Acuna promptly cured 5 syphilitic infants with mercurial treatment, and then with equal success cured 3 other infants who also had incessant vomiting, but without syphilis, by the same measures. Lozano (1930) in his study of habitual vomiting among nurslings concluded that syphilis is slightly more frequent among infants with hyperemesis than among normal infants, but it cannot be said that syphilis is either the sole cause or the most frequent cause of this condition.

Paroxysmal Hemoglobinuria.—This condition, in which a systemic reaction with hemoglobinuria follows chilling occurs in syphilitic children and adults, though we have only seen it in adults. Moss showed that a hemolysin is liberated in the blood which attacks red blood cells on chilling the body surface, causing *protein shock symptoms of chill, fever and prostration, with* hemoglobinuria.

Matsuo (1912) states that seven of his eleven patients had congenital syphilis, the others acquired syphilis. Hinrichsen (1943) points out the association between congenital syphilis, Raynaud' disease and paroxysmal hemoglobinuria in the older literature. There is some indication that paroxysmal hemoglobinuria is becoming much less common. Thus, in surveys of syphilitic cases Donath and Landsteiner (1905) found the condition in 9 per cent of 65 patients with dementia paralytica, Kumagai and Inoue (1912) in 20 per cent of 35 patients with tertiary syphilis, Ghezzi (1920) in 5 per cent of 85 syphilitic patients and Jones and Jones (1922) in 7 per cent of 43 syphilitic patients. Yet, Dill, Douvres and Isenhour (1930) found one case in survey of 900 syphilitics (no cases in 100 nonsyphilitic controls) and Howard, Mills and Townsend (1936) remark that the disease is seldom encountered. The more recently reported cases have been uniformly improved or arrested by antisyphilitic therapy (cf also Wenfter ad Parks 1936, Dickson

1936) Dill *et al.* remark that the rarity of the disease in modern times as compared with the older literature may result from the more satisfactory treatment of syphilis. For a description of the technic of laboratory diagnosis see any of the more recent articles just mentioned. This condition is not to be confused with paroxysmal nocturnal hemoglobinuria described by Marchiafava, Nazari, Michel and numerous other authors. (See also Stats and Wasserman, 1943.)

Syphilis and Tuberculosis in Childhood.—Vignolo-Lutati in 1914 called attention to the tuberculogummatous syndrome in heredosyphilitic children, especially as it affected the cervical lymph nodes. A fairly typical example of this type is given in Figure 456. Nasso found that heredosyphilis directly predisposes children to tuberculosis, 24 per cent of the syphilitic children presenting evidence of the disease as compared with 14 per cent of 26,500 normal children. Hertinel and Merklen believe tuberculous meningitis to be more frequent in syphilitic children.

In all interpretations of the syphilitic factor in tuberculous children the unreliability of weak positive Wassermann reactions and the nonspecificity of the arsphenamines must be borne in mind. Menninger (1933) mentions the fact that juvenile paretics who become emaciated, untidy and careless present fertile soil for tuberculosis and calls attention to Schmidt Kraepelin's (1900) report of six such cases.

Sclerema and Edema Neonatorum.—This condition occurs occasionally in heredosyphilitic infants, as a hardening and edema of the body fat, with subnormal temperature, coming on this the first few days after birth. The skin is thickened, lardaceous, pale and stiff, the lower extremities being most affected. The cases are usually fatal, and not generally recognized as of syphilitic origin. In two cases seen with the late F. G. Harris, and in one of our own, the recovery under mercurial inunctions was rapid and complete. All three children had heredosyphilis, and the one which appeared on J. H. S.'s service was the child of a woman who because of thorough treatment and prolonged freedom from signs had been permitted to become pregnant.

THE TREATMENT OF FAMILIAL AND PRENATAL SYPHILIS

General Principles.—The value of treating the syphilitic pregnant woman to prevent congenital syphilis, recognized since the middle of the seventeenth century, has never been more conclusively demonstrated than in the last twenty five years. Studies conducted in this country by Williams (1920, 1922), McCord (1930, 1935), Jeans and Cooke (1930), McKelvey and Turner (1934), Cole *et al.* (1934, 1936), Halloran (1939), Dill, Stander and Isenhour (1940), Benensohn (1942), by Boas and Gammeltoft in Denmark, by Nabarro and Findlay in England, by Hoffmann in Germany and by many other authors too numerous to mention, have shown that, from the therapeutic standpoint, syphilis transmitted from parent to offspring is practically a preventable disease (see Fig. 846). Its prevention rests upon the diagnosis and treatment of syphilis complicating pregnancy. Treatment to be effective must be with a strong spirillicide such as neoarsphenamine or an arsenoxide (mapharsen). For an outline of general principles see Figure 847 and for a suggested treatment course to use in the uncomplicated case see Figure 848.

Treating the syphilitic mother to preserve her child is reputed to have been first advised and carried out in France in about the middle of the seventeenth century. At this time Garnier, because pregnant syphilitic women were refused admission to the lying-in hospitals in Paris, proposed to house them in a separate hospital, feeling that, contrary to the then current opinion, treatment with mercury rubs would cure them and their children. The value of the treatment was recognized by Mauriceau (1695), became generally used in the eighteenth and nineteenth centuries as recorded by Astruc (1754), Mahon and Lamauvem (1804), Bertin (1810), and is enthusiastically reported upon by the elder Fournier (1880, 1891, 1906). Mercury and even bismuth, while producing some beneficial effect on the syphilitic fetus, have now been almost completely replaced by the trivalent arsenical drugs, which when properly administered prevent the transmission of the infection from parent to offspring in virtually every case.

Results of Treatment.—An examination of Figure 846 shows that the untreated syphilitic woman will give birth to a normal nonsyphilitic child in

Fig 846.

RESULTS OBTAINED BY SELECTED AUTHORS SHOWING PROTECTION OF THE CHILD BY TREATMENT OF THE PREGNANT SYPHILITIC MOTHER

Author	Year	Cases.	Treatment given mother	Percentage normal children.
Benesohn.	1942	789	Neoarsphenamine and bismuth.	93 5
		140	None.	60 0
Mowley Callaw y and Sharpe.	1940	21	Neoarsphenamine before and during pregnancy	100 0
		66	Neoarsphenamine during pregnancy only	90 9
		17	Neoarsphenamine before pregnancy only	88 2
		46	None.	35 6
Halloran.	1939	84	More than 10 weekly neoarsphenamine.	92 9
		140	6 to 10 wks. neoarsphenamine.	79 9
		264	less than 6 wks. neoarsphenamine.	72 4
		16	None.	18 8
Cole *et al.* (CCG)	1934	131	Trivalent arsenical and heavy metal begun before fifth month.	78 4
		30	Same as preceding but more than 10 weeks trivalent arsenical.	90 7
		132	Same as preceding but begun after fifth month.	60 6
McKelvey and Turner	1934	18	Arsphenamine during pregnancy 4 to 6 Gm.	100 0
		33	Same 3 to 4 Gm.	87 5
		65	Same 2 to 3 Gm.	83 8
		127	Same 1 to 2 Gm.	79 7
		113	Same less than 1 Gm.	73 0
		288	None.	35 4
McCord.	1930	95	More than 6 weekly injections neoarsphenamine plus mercury inunctions.	91
		94	Less than 6 weekly injections as above.	57
		137	None.	20
Gammeltoft.	1923	7	Arsphenamine before and during pregnancy	85 8
		36	Arsphenamine during pregnancy	80 7
		26	Arsphenamine before mercury during pregnancy	73 1
		111	Mercury during pregnancy	28 0
		15	Arsphenamine before, no treatment during pregnancy	20 0
		301	None.	3.5
Williams.	1920	163	4 to 6 injections arsphenamine and mercury	92 6
		103	2 to 3 injections arsphenamine.	63 0
		137	None.	47 0

PREVENT OR CURE CONGENITAL SYPHILIS BEFORE BIRTH

from 3.5 per cent of cases (Gammeltoft) to 60 per cent of cases (Benensohn) depending upon the type of material surveyed the criteria used in the diagnosis of congenital syphilis in the offspring and the duration of observation of the child after birth The improvement of statistics in recent years is probably accounted for by the increasing numbers of syphilitic women receiving treatment prior to conception All of the studies cited with the exception of those of Gammeltoft show better than 90 per cent normal children when the trivalent arsenicals are used in sufficient amounts, and some authors have obtained 100 per cent success in small series. The best results have been obtained when treatment is given both before and during the pregnancy but, since the fetus often is not infected until close to the time of delivery it is never too late to begin treatment. A satisfactory outcome can usually be expected if it is possible to start arsenical therapy by the twentieth week, and active treatment is continued until the time of delivery

Fig 847

PRINCIPLES OF TREATMENT SYPHILITIC PREGNANT WOMAN

1 Begin treatment of the syphilitic pregnant woman as soon as the diagnosis is established. A delay of even few days may mean a syphilitic child.

2. T be effective the drug must be spirillicidal. Intravenous neoarsphenamine and mapharsen are the drugs of choice. The heavy metals (mercury or bismuth) have relatively much less protective effect for the fetus.

3. Protection of the child is the primary aim of treatment during pregnancy Maternal syphilis must be cured after delivery

4. Treat largely with arsenical during the late months, largely with heavy metal during the early months. The fetus is seldom infected prior t the 20th week.

5. Reduce the initial dose of arsenical if treatment is begun after the fifth month The first injection may be 0.2 Gm. of neoarsphenamine (or its equivalent) the average dosage for the first three eeks should not exceed 0.3 Gm. neoarsphenamine per eek. Total weekly dosage need never exceed 0.45 Gm. for the 150-pound adult.

6. Continuous alternating is preferred to concurrent treatment.

7 After the fifth lunar month the length of the bismuth course should not exceed 4 to 6 weeks, lest infection of the fetus result from lack of spirillicide

8. T eatment should be continuous. No rest interval.

9. Arsenical should be given for 4 to 6 weeks immediately before delivery

10. If reactions occur stop treatment and reevaluate. Do not injure the mother from the overzealous applications of treatment for the unborn child. The average pregnant oman tolerates normal antisyphilitic therapy ell, but should reactions occur they may be serious nd should not be considered lightly

A number of investigators have remarked upon the small amount of arsenical therapy necessary t protect the child in the verage case Cole *et al.* (CCG) (1931) have pointed out that ... eeks of arsenical therapy begun before the m lpoint of the pregnancy is sufficient to produce 91 per ce t satisfactory results. Figure 819 illustrates one of the 9 per cent who are not protected by thi amount of therapy Findlay (1942) remarks that, in his experience healthy child has always been born hen treatment as begun before the beginning of the eighth month of pregnancy While this latter viewpoint is certainly an underestimat of the amount of treatment necessary t protect the child, yet there is every evidence that it is unnecessary to overburden the pregnant woman by using large dosage of the drug or to give injections ith more than the usual frequency in order t obtain a healthy child.

It should be noted that proper evaluation of therapy both in the prevention of congenital syphilis by treating the pregna t oman and in the treatment of the syphilitic child, has been confused by failure on the part of most authors t use normal control series in interpreting the results of pregnancy and by variations in the criteria employed for the diagnosis of the infection in the child and occasionally even in the mother Dill, Stander and Isenhour (1940) are virtually

the only recent authors who have used control series of normal pregnant women in the evaluation of their results.

Technic of Treatment of the Pregnant Woman.—For adequate protection of the fetus, the dosage of arsenical need not exceed 0.45 Gm. of neoarsphenamine or its equivalent (see Fig. 848). Minnich (1941) has shown that mapharsen in dosage up to 0.05 Gm. once weekly is as effective as neoarsphenamine

Fig. 848.

TREATMENT OF PREGNANCY WITH LATENT SYPHILIS OF UNKNOWN DURATION (UNCOMPLICATED)

(Modified from Stokes and Ingraham, Medical Clinics of North America, November 1930.)

Week of pregnancy	Lunar month. 1 to 4	5	6	7	8	9
1 to 16	varying amount NS & Bi					
17	Bi, 0.2 Gm.	NS, 0.2 Gm.				
18	Bi	NS, 0.3				
19	Bi	NS, 0.4				
20	Bi	NS, 0.45				
21	NS, 0.45 Gm.	NS, 0.45	NS, 0.2 Gm.			
22	NS	NS, 0.45	NS, 0.3			
23	NS	NS, 0.45	NS, 0.45			
24	NS	NS, 0.45	NS			
25	NS	Bi, 0.2 Gm.	NS	NS, 0.2 Gm.		
26	NS	Bi	NS	NS, 0.3		
27	NS	Bi	NS	NS, 0.4		
28	NS	Bi	NS	NS, 0.45		
29	Bi, 0.2 Gm.	Bi	Bi, 0.2 Gm.	NS	NS, 0.2 Gm.	
30	Bi	Bi	Bi	NS	NS, 0.3	
31	Bi	NS, 0.45 Gm.	Bi	NS	NS, 0.45	
32	Bi	NS	Bi	NS	NS	
33	NS, 0.45 Gm.	NS	NS, 0.45	Bi, 0.2 Gm.	NS	NS, 0.2 Gm.
34	NS	NS	NS	Bi	NS	NS, 0.3
35	NS	NS	NS	Bi	NS	NS, 0.45
36	NS	NS	NS	Bi	NS	NS
37	NS	NS	NS	NS, 0.45 Gm.	NS	NS
38	NS	NS	NS	NS	NS	NS
39	NS	NS	NS	NS	NS	NS
40	NS	NS	NS	NS	NS	NS

NS = neoarsphenamine
Bi = bismuth subsalicylate
Dosage is calculated for 150-pound individual.

There is some evidence to indicate that mapharsen or other arsenoxide given in one tenth the above dosage every five instead of every seven days is also effective.

and possibly better tolerated. Castallo, Coppolino and Rakoff (1950) had, however, obtained less satisfactory results with this drug. It is probable that mapharsen should be given every five days to the pregnant woman to obtain maximum beneficial effect for the fetus. *Intramuscular arsenical preparations* (*e.g.* bismarsen) *are not effective* (Benensohn, 1942) and should not be used in the treatment of the pregnant woman. Some authors have reported the successful use of intensive arsenical therapy five-day drip in the pregnant woman

with early syphilis (Rattner 1943 Sadusk and Shaffer 1942) but considering the excellent results normally obtained with more conservative treatment, as well as the increased risk to the mother when the more intensive methods are employed we do not consider that they are indicated.

Some discussion and difference of opinion have centered about the question of the use of an arsenical and bismuth preparation concurrently particularly if treatment is not commenced until the latter months of the pregnancy Although this type of treatment has been used successfully by some authors and has been recommended by McKelvey and Turner (1934) Hoffmann (1938) and Benensohn (1942) the fact that the heavy metals have relatively little protective effect for the child makes this seem unnecessary especially when the use of heavy metal concurrently increases the risk of complication for the mother

Cole et al. (CCG 1934) found that mild reactions from arsenicals were more frequent when combined therapy was employed. The increased frequency these authors state, was especially noted in transient kidney irritability it being seven times as common with combined as the alternating therapy McKelvey and Turner (1934) found that when the mother received some heavy metal during her pregnancy the child was normal in 93 4 per cent of cases as compared with 78.0 when only arsenical was used, but did not control the duration of treatment in their series, which could be factor of considerable importance They state that those patients who received heavy metal were in general those who had reported early in pregnancy

Control of Treatment Reactions.—Antisyphilitic treatment during pregnancy should be accompanied by more than ordinarily careful obstetrical prepartal care. Ingraham Ingraham Beerman, Spence, Arnold and Hasler (1941) have pointed out the desirability of conducting separate clinics for the pregnant syphilitic woman where this is practical in the larger urban hospitals. These patients should have frequent, preferably weekly urine analyses and should have physical inspection by a physician and questioning concerning symptomatology which might indicate circulatory or kidney strain, incipient toxemia, or intercurrent infection producing fever before each treatment. Blood pressure should likewise be taken at each visit. Blood and platelet counts should be available in reactive patients.

While it is difficult to set arbitrary rules, and individual case problems should be decided upon only after competent obstetrical and syphilologic consultation in general treatment should be withheld until competent appraisal of the situation is possible (1) if the woman s blood pressure, which has been normal, increases to exceed 150/100 (2) if vaginal bleeding, hematuria, purpura or other hemorrhagic phenomena (hematopoietic injury) occur (3) if there is jaundice or other evidence of liver damage (4) if severe headache visual disturbances or other evidence of central nervous system involvement become manifest (hemorrhagic encephalopathy) or (5) if the woman reports with a temperature of more than 100° F

With normal precautions, standard treatment as outlined in Figure 315 may be given without hesitancy to the pregnant woman. When complications of syphilis occur (as e g cardiovascular involvement) treatment of this stage of syphilis, as described in the preceding chapters, takes precedence over the protective treatment for the child When special types of treatment are indicated (as fever therapy for central nervous system involvement) these had best be postponed until after the termination of the pregnancy continuing normal protective treatment for the child until delivery occurs. In general,

spinal fluid studies also should be postponed until after delivery Tryparsamide should be withheld since its effect on the optic tract of the fetus is unknown.

A considerable literature has accumulated in the last few years on the subject of treatment reactions in syphilitic pregnant women, and a number of deaths, usually from acute hemorrhagic encephalitis have been reported (*cf* Ingraham, 1939, Moore, 1939, Kennedy and Healington, 1943) As a rule, these complications are treated as in the nonpregnant adult as described in previous chapters.

A word of caution should be interjected concerning the diagnosis of acute hemorrhagic encephalopathy in the parturient woman because, not infrequently in the past, these cases have been considered and treated as toxemias of pregnancy until the terminal and hopeless stage of coma and convulsions was reached or until death had occurred and the correct diagnosis was revealed by autopsy Toxemias of pregnancy are no more frequent in the treated syphilitic than in the nonsyphilitic woman (Peckham, 1941). Eighty-one per cent of the cases of acute hemorrhagic encephalopathy collected by Ingraham (1939) were precipitated by three or less arsenical injections. Everyone who treats syphilitic pregnant women should be familiar with the premonitory signs of acute hemorrhagic encephalopathy in order that recognition and treatment may be immediate should it occur Pregnant women are also said to present an increased susceptibility to severe liver damage as a result of antisyphilitic therapy but we have never personally seen such a case.

Collateral Aspects of the Treatment of Syphilis and Pregnancy—It has been advised by some writers that pregnant women be treated on the mere suspicion of syphilis that the expectant mother be treated if her husband has syphilis that active syphilis complicating pregnancy may be an indication for inducing abortion that a woman once syphilitic should be treated through each subsequent pregnancy that the syphilitic mother should not nurse her infant after delivery We would like to say a few words about each of these points.

With present day diagnostic standards, there is no reason to treat a pregnant woman for syphilis unless she is definitely known to have or to have had the disease. Inadequately treated seronegative syphilitic women, who may still give birth to diseased infants unless proper therapy is instituted, may form something of a diagnostic problem and point out the need for careful history taking and careful physical examination supplemented by complete family investigation when indicated.

The Follow-up of the Syphilitic Family—The detection of a family focus calls at once for the medical examination of every member Pressure to secure this should be first brought by the physician. While the problem may present difficulties in private practice, it should, nonetheless, be systematically attempted.

Ingraham (1938) has pointed out that even assuming an almost perfect medicotherapeutic approach to the problem of congenital syphilis control, three problems of social and public health administration still block full accomplishment in this field (1) the pregnant woman with syphilis often does not report for prenatal supervision until late in her pregnancy when infection of the fetus may already have taken place (2) a delay of some weeks between the initial antepartum visit and the commencement of antisyphilitic treatment is a common occurrence. This interval should never be more than a few days; (3) congenitally syphilitic offspring are frequently not treated in early infancy Treatment could always be started in the first few months of life if proper diagnostic procedures are carried out.

The premarital laws and routine blood test procedures previously discussed have many pitfalls for the unwary Bedard (1940), in citing three instances in which seronegative syphilitic mothers in whom the disease remained undetected and untreated prior to delivery gave birth in each case to a syphilitic child, asks with some justification: "Why not Wassermannize the expectant father?"

Since the mother frequently escapes infection even though the father may be syphilitic, and since infection of the fetus is via the placenta and not from

the seminal fluid there seems to be no reason to treat the pregnant woman merely because her husband is diseased. Occasional cases are seen in which the husband has acquired or the wife has been exposed to infectious syphilis during her pregnancy We have found it satisfactory to withhold treatment in such cases until infection if present, is proven in the expectant mother performing the same type of routine medical and serologic follow-up as with any other patient who is known to have been exposed to infectious syphilis.

Syphilis in itself is no reason for interference with the pregnancy of a syphilitic woman. From the standpoint of the mother carrying the pregnancy to term may be conceived as a reinforcement of her defense mechanism, of which she should take full advantage. Moreover the treatment of the mother during pregnancy protects the child in such a large proportion of cases that it seems unjustifiable to take its life merely on the small chance that it may turn out to have syphilis. Even if the child does show evidence of syphilis after birth, the outlook for health following effective treatment is good enough to justify its being given the chance for life

Conservative opinion suggests that with our present day knowledge, a syphilitic woman should be treated through every pregnancy, regardless of the duration of her infection, her serologic status, or the amount or type of antecedent therapy Treatment in any instance should be given only if well tolerated as described above

The reasons for this conclusion are as follows (1) Instances are known in which syphilitic women have given birth to diseased children as long as twenty years after they have acquired the disease. While a syphilitic woman with disease of long standing is less likely to give birth to a diseased child than one who has recently acquired her infection this is a factor of only relative importance and cannot be used as a basis for decision with respect to therapy (2) There is no diagnostic test which will insure that a pregnant woman (or any other individual for that matter) is completely free from the disease after she has been known to have acquired it. The relationship between mother and fetus is more intimate and for a longer period of time (nine months) than we meet under any other circumstance Even a transient spirochetemia may result in infection of the placenta and subsequently of the unborn infant. (3) As yet, there have been reported no extensive series of mothers clinically cured of the disease who have gone through subsequent pregnancies untreated to make a proper evaluation of complete treatment possible with respect to risk for the fetus in subsequent pregnancies. It is to be hoped that a more complete evaluation of some of the more intensive systems of treatment prior to conception may make some modification of this position possible.

Birnbaum (1927) has reported series of twenty-one women in whom syphilis was cured by appropriate treatment They later had thirty-four pregnancies, untreated all the while, which resulted in apparently normal children who remained free from syphilis, some for as long as six years at the time of publication.

Cole et al (CCG 1931) found that in fifty-two women ho became pregnant after being considered cured, their data did not furnish evidence of syphilitic child having resulted although births occurred up to fifteen years after the infection. McKelvey nd Turner (1931) reported in their series fifty-nine pregnant omen who had received minimum of 1 Gm. of arsphenamine prior to pregnancy but no treatment during the pregnancy none of whom gave birth to children with evidence of syphilis Rattner (1915) states that five patients of his series who had been treated by the five-day method, subsequently became pregnant and though no additional treatment was given, each has given birth to normal infant. Findlay's (1914) experience with adequately treated seronegative syphilitic mothers is such as to make him feel that "it is difficult to understand how

most writers recommend that further courses of salvarsan therapy should be carried out through any succeeding pregnancy

An essentially similar question is that as to whether a congenitally syphilitic woman who reaches adult life should be treated during her pregnancy In general we feel that the answer to this is *no* provided previous treatment adequate to control the activity of the congenital infection (not necessarily *to reverse the blood serologic test to negative which cannot be accomplished* in every instance) has been carried out. When confronted with a congenitally syphilitic woman who is pregnant we carefully review the previous medical handling. If this has been sufficient to prevent the development of interstitial keratitis (sixteen weeks of arsenical and thirty-one weeks of heavy metal after Cole *et al.*, 1937) and if there is no active central nervous system involvement we advise withholding therapy during pregnancy and observing the child postnatally If previous treatment has not been adequate, we advise treatment throughout the pregnancy more for the sake of the mother than the child. Third generation syphilis is excessively rare as discussed in a previous section

As a rule, if she has no infectious lesions a syphilitic mother may nurse her newborn child. We have never seen an exception to this statement, although Uhlenhuth and Mulzer (1913) have demonstrated *Spirochaeta pallida* in the mother s milk. It is necessary of course, that the mother with active syphilis be receiving treatment for her disease. Moore (1941) cites instances in which each of two infants developed a chancre of the lip through neglect of this precaution. Instances in which either mother or child has acquired the disease independently after birth may of course result in infection of the uninfected individual through nursing, and artificial feeding should always be resorted to in such cases.

The question occasionally arises as to whether antisyphilitic therapy given the mother prenatally may ever be harmful to the fetus. In general, we may state that the *amounts of arsenical and heavy metal which traverse the placental barrier with normal treatment are not injurious to the unborn child.* There has been considerable discussion in the older literature concerning placental shock (miscarriage resulting from arsenical therapy) When the fetus is already dead or grossly diseased introduction of arsenical therapy may result in sufficient reaction in the placenta to cause premature labor but this is seldom, if ever the case when the fetus is not grossly infected.

Type Cases *Management of Syphilis in Pregnancy* —*It is possible from* our general knowledge of syphilis to classify to some extent the treatment problems presented by the pregnant syphilitic woman, and to govern her treatment accordingly It must be remembered that in general the newly infected mother will not appear for treatment until florid eruptive manifestations have developed whether early or late in pregnancy

1. **Infection Coincident with Conception or Occurring Within the First Few Weeks of Pregnancy Chancre Present Blood Serological Reactions Negative.**—Such a situation, the most dangerous of all for the child, justifies also an attempt at radical cure of the mother for her own sake and that of her future pregnancies. The risk of inducing abortion by the use of a neoarsphenamine-bismuth system with five- to seven-day intervals at the outset is not great in our experience, though Buschke complained of abortions from the arsenical and by the time the pregnancy is far enough advanced to demand all her physical resources, two short (8-injection) courses each of arsenical and

heavy metal can have been given. Suppression of the infection without cure or with *postpartum* relapse must be guarded against by observation of mother and child and by the continuance of the mother's treatment through the full regimen for an early acquired infection and if possible up to the very end of the pregnancy. Should she in subsequent pregnancies be advised to take prophylactic treatment, even though supposedly radically cured? In our present knowledge of the problem the answer is yes.

2 **Woman Appears with Florid Secondary Syphilis Within the First Six Months of Pregnancy.**—In all fully developed infections in early pregnancy the mother whose condition is normal can sustain a moderate course of treat-



Fig. 849.—An illustration of the occasional failure of prenatal treatment of the mother to protect her child from uterine infection, and of the comparative robustness of a nonrelapsing syphilitic child. The mother received 10 injections of neoarsphenamine and 6 of bismuth between the fourth and eight months of pregnancy having entered with secondary syphilis. The child's cord Wassermann was positive, all subsequent tests negative until at seven months of age the eruption shown above appeared when the serological tests became positive.

ment for syphilis. No attempt should be made to shorten intervals and raise dosage beyond half the adult maximum. The treatment course should be so planned that the mother receives neoarsphenamine during the last two months of her pregnancy.

3 **Primary Lesion and Negative Blood Serologic Test in the Last Three Months of Pregnancy.**—In a case of this sort strenuous measures for radical cure are not justifiable for they may endanger both mother and child. Two-thirds the maximum adult dosage of neoarsphenamine intravenously once in five to seven days with a few injections of bismuth or small mercurial inunctions will protect both mother and child so far as our present knowledge goes. There need be no rest period allowed up to within a week of term.

4 **Florid Secondary Lesions and Positive Blood Serologic Test Developing Within the Last Three Months of Pregnancy**—Neoarsphenamine of known therapeutic effectiveness should be the mainstay and the later the pregnancy the less need is there for the intensive use of heavy metal. Immediately *postpartum* in these cases and the foregoing group, bismuth and arsphenamine should be pressed to forestall neurorecurrence or infectious relapse. Inasmuch as the child will have an outlook for complete escape, the closest attention should be paid to recurrence in the mother by both serological control and clinical examination, and the child should not be put to the breast unless the mother continues arsphenamine treatment.

5 **First Pregnancy in a Mother With Latent Syphilis of One to Five Years' Duration, Blood Serologic Test Positive.**—In this type of case the 8 to 10 injection neoarsphenamine course with weekly intervals between injections may be begun as soon as the patient comes under observation. Two arsphenamine courses alternating with bismuth timed so as to bring the patient to term while still receiving arsenical, and with the mercury or bismuth not later than the eighth lunar-month, may be arranged if time and condition permit.

6. **Multipara (More than Three Previous Pregnancies Carried Beyond the Seventh Month), Blood Serologic Test Positive.**—The protective effect of previous pregnancies if they occurred after infection may be anticipated and a single course of 8 to 10 injections neoarsphenamine in the latter half of the pregnancy preceded by bismuth and carried to term should protect the child. There is, however some doubt as to whether the arsenical should not be more prolonged if used at all.

7 **Woman Known to Have Had Syphilis, but Apparently Cured. 'Treatment for Life Insurance.''**—This is, of course, the type of case which lies just beyond the border of knowledge at the present time. We advise a 10-injection course of bismuth followed by an 8-injection course of neoarsphenamine "stretched to cover the last ten weeks to term and followed by bismuth intramuscularly for three months *postpartum*.

Postpartum Observation.—Adequate *postpartum* observation of both mother and child is a paramount obligation. None of the results as yet published can in point of time alone, answer finally the question as to whether the seemingly well child is actually well. The critical years, seven and fourteen, second dentition and puberty must be safely passed in a considerable group of cases before treatment of the mother can be evaluated for the child Under the conditions of public clinics a year or two of observation is all that most observers feel can be expected for the rank and file, but every effort should be made to extend this by those who have opportunity Nothing more than encouragement and evidence of symptomatic rather than curative effect can be drawn from the usual maternity service reports which embrace the condition of the child ten days to two months after birth.

Indications for Treatment of Congenital Syphilis in the Newborn Infant.—Recent developments in the diagnosis of infantile congenital syphilis make a brief summary of the diagnostic criteria desirable. In general, treatment should not be given unless a diagnosis of the disease is established in the infant.

Black (1930) has given an interesting summary of the pathognomonic criteria in the diagnosis of congenital syphilis. Ingraham (1935) has summarized from the literature the pros and cons for treating the apparently healthy offspring of syphilitic parentage without establishing definite diagnosis of syphilis in the infant. One of the strongest proponents of treating every in-

fant of syphilitic parentage at birth irrespective of antepartum handling is Hoffmann (1936). He feels that in resorting to such practice we are merely continuing therapy commenced via the placenta before birth. Perhaps the strongest argument against such procedure, of the several collected by Ingraham, is the fact that, as a result of treatment of the mother before birth, congenital syphilis is becoming so uncommon, that if treated all offspring of syphilitic parentage on the theory that they might be infected we would be treating largely normal children. Ingraham and Kahler (1934) have especially cautioned against the practice of treating infants of syphilitic mothers for a few weeks after birth, and then dismissing them, with or without periods of observation, if they remain symptom free. Such a procedure would succeed largely in curing those infants who did not have the disease and would give false sense of security to those cases be are harboring the micro-organism.

Many of the writings of a decade or more ago which attempt to evaluate the success of treatment of the pregnant woman or the infant with congenital syphilis have been rendered of little value by failure to understand the diagnostic criteria about to be summarized. We again emphasize that the adequate detection of congenital syphilis in infancy depends upon a knowledge of the existence of maternal syphilis and that the study of the mother must precede the study of the infant. The offspring of a syphilitic mother may be considered to be infected and eligible for treatment when

1. *Spirochaeta pallida is demonstrated* in skin or mucous membrane lesions or in scrapings from the umbilical vein.

2. *The blood serologic test for syphilis* is strongly positive on repetition *after the third month of life*. Prior to the third month, in the absence of clinical symptoms it is difficult to establish a definite diagnosis without a knowledge of the mother's and infant's serologic test at birth and without the use of *quantitative titered tests*. If such information is available then the following additional criteria for diagnosis are applicable.

(*a*) the titer of the blood serologic test of the infant is significantly greater than that of the mother (or positive when the mother's test is negative).

(*b*) the titer of the infant's blood serologic test rapidly increases after birth (or a test negative at birth subsequently becomes repeatedly positive).

3. *A properly interpreted roentgenogram* in a seropositive infant during the first eight weeks of life shows an unquestionable (preferably advancing) osteochondritis with or without periostitis.

Management of the Syphilitic Infant.—In general, a considerable pessimism has marked the literature on the treatment of syphilis in infancy and childhood especially in England and this country. This has arisen in large part from the fact that the disease so frequently developed symptomatically before it was recognized and treatment instituted. With the better management of the syphilitic pregnant woman and the wider application of the serologic test and roentgenogram in early infancy, the clinical cure of early congenital syphilis at least is becoming easier so that crippling and death from congenital syphilis at this age are the exception rather than the rule. The principles in the treatment of the syphilitic infant are summarized in Figure 850.

Persistence in therapy is necessary, at the same time controlling initial dosage carefully to correspond with the severity of the infection, in order to avoid damage from therapeutic shock or paradox. It is hard to escape the feeling that, in the past, too many clinicians have been too conservative, timid and not sufficiently persistent in their treatment of the syphilitic child. Early prenatal syphilis is virulent syphilis. The issue at stake is the child's life, and it seems better to adopt adult intensity in treatment even at some

risk than to give single courses or short (half) courses separated by long intervals of rest. The response to neoarsphenamine is known to be good and bismuth can be given, or mercury by inunction. Full weekly dosages of drugs commonly employed for the treatment of infantile congenital syphilis are given in Figure 851. The length and character of the treatment courses employed in the management of infantile congenital syphilis, or asymptomatic late congenital syphilis are largely the result of inference, by utilizing methods which have been found applicable in the management of adult syphilis. Treatment is ordinarily given in alternating courses of arsenical and heavy metal of six to ten injections each over a period of about one year. Before

Fig. 850.

PRINCIPLES IN THE TREATMENT OF INFANTILE CONGENITAL SYPHILIS

1. Do not begin treatment until the presence of the disease in the infant is established beyond question.

2. With definite diagnosis no infant is too small or too young to treat, with appropriate dosage of the drug.

3. With premature or malnourished infants every attention should be given to improving the physical condition by general medical care, but antisyphilitic treatment should not be withheld until the nutritional state improves.

4. Injection therapy is preferable to mouth medication or to mercury rubs, because of the greater ease in controlling dosage. A soluble heavy metal is preferable to an oil-suspended preparation for the same reason.

5. Because of the severity of the infection as it often occurs in the small infant, therapeutic shock and therapeutic paradox are to be feared, and may result in severe injury or even death of the infant if they are permitted to occur by injudicious choice of drug or too large dosage.

6. For this reason it is usually better to begin treatment with heavy metal rather than an arsenical and it is preferable to use from one-fourth to one-half the dosage calculated for the weight of the infant for the first two weeks, increasing to full dosage after the first month.

7. Dosage should be accurately measured for small infants in a tuberculin syringe with proper dilution of the drug.

8. Treatment should be continuous without rest interval for about one year if response is normal.

With newborn infants, the individual dosage of bismuth metal may be so small that with the normal concentrations of the standard preparations, accurate measurement may not be possible without dilution. With water soluble preparations this is easily accomplished, but with oil suspended preparations more difficulty is encountered. Active hospital services, where infantile congenital syphilis is a *frequent occurrence*, will find it profitable to have prepared in advance an oil suspended bismuth subsalicylate containing 20 mg. of bismuth metal per cubic centimeter by diluting the standard preparation with sterile olive oil or peanut oil.

the treatment is terminated a spinal fluid study should be performed. If both blood and spinal fluid examinations are normal, a year's treatment is considered to be sufficient. If the blood remains positive an additional six to twelve months of treatment are given, followed by a period of observation, preferably covering the next several years, but no more treatment is necessary unless symptoms of progression develop. Central nervous system involvement or ocular complications require special handling for which see subsequent sections. This is the type of therapy which we have used with good results both at the University and the Philadelphia General Hospitals. It is similar to that employed by Smith (1935), Cole (1937, 1941), Robinson (1937), Yampolsky (1938) and Howard (1939).

Choice of Drug—The choice of an arsphenamine in the treatment of prenatal syphilis will often be a matter of circumstance rather than pure therapeutic indications. **Neoarsphenamine** intravenously is readily available to the reasonably expert and, on the whole is satisfactory. Nothing compares in rapidity with the transformation brought about by "606" and "914." Arsphenamine is virtually never used at the present time in the treatment of infantile congenital syphilis because of the difficulty in its preparation and only rarely in late prenatal syphilis. Morgan (1938), Howles (1939) and Astrachan and Cornell (1943) have all reported upon the successful use of mapharsen in the treatment of congenital syphilis. Levin, Hoffman, Korasky, Richter and Gumbiner (1942) have used five-day intravenous drip with mapharsen in congenital syphilis, but favorable results were obtained in only 12 (37.5 per cent) of 32 patients. Dosages employed ranged from 1.6 mg. to 3.0 mg. per pound of body weight per day. Givan and Villa (1939) reported

Fig. 831

FULL WEEKLY DOSAGE OF DRUGS COMMONLY EMPLOYED IN TREATMENT OF INFANTILE CONGENITAL SYPHILIS BY INJECTION

(Initial dosage in active infections should be from one fourth to one half the amounts given below.)

Drug	Dosage (mg. per pound body weight)
Arsphenamine	3-4
Neoarsphenamine	5-8
Trisodarsen (trisodium arsphenamine sulfonate)	5
Mapharsen (meta-amino-parahydroxyphenylarsine oxide)	0.4-0.5*
Sulpharsphenamine	5-10
Bismarsen (bismuth arsphenamine sulfonate)	6
Bismuth (in terms of bismuth metal)	1-2†

* Experience in the use of mapharsen in the treatment of congenital syphilis is limited. There is feeling on the part of some that this dosage should be given at five-day rather than weekly intervals.

† Bismuth preparations vary greatly in content of metallic bismuth. If water-soluble preparation is employed one half this dosage should be given twice weekly.

the use of trisodium arsphenamine sulfonate (Trisodarsen) in the treatment of congenital syphilis with therapeutic results similar to those obtained with other trivalent arsenicals. Sulpharsphenamine, in a dosage of 20 mg. per kilo, has established itself with a number of observers as an effective drug, and the strong objections to its use in adults, because of the complications it produces, do not seem to be so applicable in the infant, who tolerates it better. Bismuth arsphenamine sulphonate has appealed to us as a moderately effective but not particularly impressive agent for the treatment of active tardive prenatal syphilis. It reverses approximately half the apparently fixed positive serological cases, but in interstitial keratitis is too slow and is comparatively ineffective in prenatal neurosyphilis. Beerman, Shaffer and Livingood (1942) conclude that bismarsen seems to be of value for the average patient with congenital syphilis. When used with infants, if response is normal, it may be continued with dosage recommended in Figure 831 for approximately

forty weeks without rest interval, terminating treatment with twelve weeks of bismuth subsalicylate.

The use of *acetarsone* in the treatment of syphilis in childhood is discussed in Chapter VII but is not recommended.

Bismuth in prenatal syphilis in infants is used as an adjunct to the arsenical much as in the treatment of adult syphilis. While it has largely supplanted mercury in all stages of the disease it is rarely used alone with satisfactory results. Wright has used bismuth alone successfully in the treatment of late congenital syphilis in certain stages.

Technic of Treating the Infant.—By the skilled technician, neoarsphenamine, and mapharsen, will be given intravenously in even the small infant by the technic described on p. 317 The jugular veins, scalp veins, and antecubital veins are all suited to this purpose. The frontal sinus should never be used. The less skilled will give the arsenicals intramuscularly or under the fascia in the parietal region of the scalp (Cole 1937) Bismarsen and sulph arsphenamine should be given only intramuscularly but it should be pointed out that the dosage for the infant under one year of age is so small that any of the arsenical preparations may be given intramuscularly Yampolsky (1938) in particular has remarked upon the use of neoarsphenamine intramuscularly in infants and Astrachan and Cornell (1943) upon the use of intramuscular mapharsen. Our experience is in accord with that of Robinson (1937) to the effect that concentrated solutions are better tolerated by intramuscular technic than are dilute ones. For intramuscular use the drug for the small infant need seldom be dissolved in more than 0.5 to 1 0 cc. of solvent. It is important to empty the needle by an air bubble with those small doses.

Reactions from Antisyphilitic Therapy in Infants.*—Aside from therapeutic* shock and therapeutic paradox which may be more serious problems with infantile than with adult syphilis, treatment reactions and their management follow the same general pattern as described in previous chapters. We have personally seen two instances of acute yellow atrophy of the liver, apparently from sulpharsphenamine resulting in the death of the infants treated at the age of five months and seven months respectively

Wolman (1940) has reported two cases of acute necrosis of the liver with death at the age of six weeks and nine months respectively following the administration of sodium bismuth thioglycollate (thiobismol) The older of these patients had also received sulpharsphenamine. In neither of these infants had a definite diagnosis of congenital syphilis been established which leads the author to remark, "One cannot condemn too strongly such a tendency to administer therapy to newborn offspring of infected mothers before signs of congenital disease become evident.

Friedman and Shinefeld (1941) report two cases of fatal hemorrhagic encephalopathy at the age of eight months and fourteen months respectively following sulpharsphenamine therapy One of these infants likewise probably did not have syphilis.

Infectiousness.—The syphilitic infant in florid eruption may be a source of infection and should be handled as such, though some observers feel that the risk to ordinary contacts is small. The early institution of arsphenamine treatment soon does away with the possibility of transmission. The congenitally syphilitic infant s ability to develop superficial infectious lesions is largely confined to the first year of life and almost never occurs after the fourth year By the time he reaches school age the possibility of transmitting

the disease to his playmates hardly needs to be reckoned with irrespective of his serologic status or amount of previous therapy

Adoption Problems.—The adoption problem of the syphilitic orphan or illegitimate child is not simple. The child should not be farmed out to an unsuspecting family or offered for permanent adoption without a full statement of the case to those who assume responsibility for it. In no case should such a child leave custodial care before it is two years old, and arrangements should be made to follow it by medical and serological examination over a period of years, if not until puberty The Welander home offers much the best solution of the problem. If a complication such as interstitial keratitis develops, adequate treatment should be provided by the state or county authorities, and the burden of a decline in independent earning capacity should not fall on the adopting family

Serological and Clinical Controls of Treatment.—The laboratory and clinical controls of treatment, both as regards the eye and general physical examination and the blood serologic test and spinal fluid examination, should be those for syphilis in general An early spinal fluid examination serves to lend direction to treatment. In no case should a child be sent out for adoption or raising without such a test. About half the patients with ordinary treatment attain and hold serological negativity of the blood and those who fail to do so should be interpreted more leniently in the absence of neurosyphilis than the acquired case. The ever present anxiety in the resistantly positive prenatal syphilitic is an outbreak or relapse of interstitial keratitis. There is, however a distinct type of prenatal syphilitic who carries a resistant positive test in robust health with no complications, probably throughout life and this type of patient, discovered in adult life, should not be overtreated, as he usually is.

The question of spontaneous remission in congenital as in adult syphilis, has been alluded to by a number of writers in recent years, and has been discussed in the light of their experience by *Ingraham, Shaffer Spence and Gordon* (1941). While the occurrence of this type of case does not alter the recommendations with respect to the adequate early treatment of every case of congenital syphilis, yet it is a factor which must be borne in mind in evaluating effectiveness of treatment.

The Management of Tardive Prenatal Syphilis.—The earlier in life treatment for syphilis can be begun, the better the ultimate result. Recent observations have even tended to show that treatment *in utero* through the mother makes even postnatal treatment of the child more effective. Tardive prenatal syphilis is, in general, late rather than early syphilis, and unless in the case of some fulminating complication can be dealt with by the more leisurely but very persistent methods adopted for the later years of the acquired form It is impossible to exaggerate the value of this leisurely but determined persistence in treatment in the securing of ultimate good results.

The basic methods used throughout the original Mayo Clinic series included (1) The repeated 6 to 8 injection arsphenamine course with simultaneous inunctions, (2) the four months interim at home on one month rest, 40 rubs and one month rest and (3) individualization of the refractory infection somewhat as indicated in Fig 338. The use of arsphenamine instead of neoarsphenamine as soon as the age of the child permits the combination with mercury by inunction and the rejection of insoluble salts; the prolonged use of moderate doses of bismuth and persistent leisurely treatment after the acute phase is controlled seem to us essential features of the technic. Bismuth in recent years has largely replaced the inunction.

Results of Treatment of Congenital Syphilis.—What such a mode of procedure accomplishes is shown graphically in Figures 853 and 854. In the former it will be seen that 82 per cent of our 170 cases achieved a good clinical result, and 62 per cent a serological reversal to negative. Only 18 per cent of our patients failed to obtain notable improvement. Serological results

Fig. 836.

EXTENSIVE OSSEOUS INVOLVEMENT IN TARDIVE HEREDOSYPHILIS WITH NEGATIVE BLOOD WASSERMANN REACTION. RESISTANCE TO TREATMENT OVERCOME BY COMBINING MERCURY AND ARSPHENAMIN AND USING ADULT DOSAGE.

Female, aged eight.

Date Examined 1/4/20.
Chief Complaint: Inherited syphilis.
History First living child. Wart developed at the anus when a few weeks old. Health good until two years ago, when an annular eruption and bilateral interstitial keratitis appeared. Six months ago the nasal bridge collapsed and painful swellings of forearm and leg developed. Perforation of the palate began six weeks ago.
Examination Parietal bosses, flat nasal bridge. Old bilateral interstitial keratitis. Hard palate inflamed and perforated. Serrated teeth, not Hutchinsonian. Osteitis of the radius and fibula. Liver and spleen palpable. Liver tender. Blood Wassermann reaction negative repeatedly (positive obtained seven months later). Previous treatment, neo-arsphenamin 15 injections, 300 mercurial treatments (rubs?)
Treatment Three courses, 8 injections each, neo-arsphenamin 0.2 to 0.3 gram. Mercury succinimid $\frac{1}{10}$ to $\frac{1}{8}$ grain. Total of 600 — 4 gram 30 grain inunctions. Nine injections $\frac{1}{4}$ grain mercury salicylate. Iodid by mouth.
Treatment Result. Complete disappearance of all osseous lesions and arrest of palate perforation, first course. Healing of gummatous septum, second course. Remarkable gain in weight and physical development. Weathered measles, sprained ankle, and fracture of formerly gummatous radius without slightest ill effect. Weight gain 44 pounds in twenty-four months.

Discussion

In spite of previous arsphenamin and mercurial treatment this patient presented an actively progressive osseous heredosyphilis. It was arrested only by
(a) Hospitalization with rest in bed.
(b) The synchronous use of mercury and arsphenamin.
(c) An arsphenamin dosage scale proportioned to the adult rather than to the child.
(d) The use of neo-arsphenamin in therapeutically and not arsenically equivalent doses.
(e) In addition to the above-mentioned factors an element of discipline was involved. This patient had previously received such treatment as she permitted her medical advisers to give her. Under kindly but firm and determined management she received the dosage and treatment which were adapted to her case.
(f) It is often extremely difficult to stop the progress of palatine perforation and to suppress gummatous osteitis of the septum and to bring a patient with this resistant type of osseous syphilis through a fracture without relapse. Gummatous recurrence is a good test of the efficiency of treatment.
Note that in spite of the active osseous syphilis and clinically undoubted nature of the condition the patient only once had a strongly positive blood Wassermann reaction. The spinal fluid is negative.
Little or no change was to be expected in the residua of the interstitial keratitis. The mother of this child has been repeatedly negative to syphilologic examination.

lag behind clinical results very definitely. Serological recurrence may be observed after several years of negative blood serologic reactions, and patients negative before treatment occasionally develop into resistant positive cases after treatment. The grading of clinical improvement is held below the best levels in a number of cases because of residua of interstitial keratitis

which mar the result. Very few patients indeed cannot be promised some degree of improvement in their general condition, and the gains in health, strength, personality and address which many of them make over a period of three or four years are most gratifying Figure 854 shows graphically the

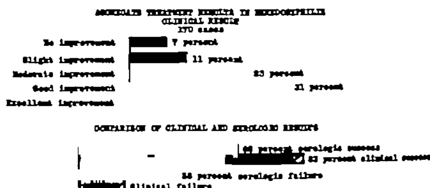


Fig 853.

relation of the grade of improvement to the number of courses of treatment received The rapid rise in excellent results with each successive course and the decline of mediocre results is an unmistakable index of the direction treatment must take in these cases.

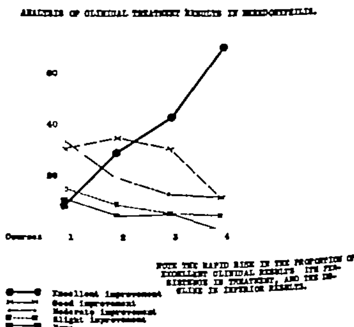


Fig 854.

Perhaps the most graphic portrayal of the results of treatment in congenital syphilis is to be found in the work of *F R Smith, Jr* (1933, 1936 based upon a study of the results of treatment in 621 patients with early congenital and 370 patients with late congenital syphilis. The earlier in 14

treatment is begun the more likely is the blood serologic reaction to become negative the better the ultimate clinical outcome and the less likely is clinical relapse to occur The tabular summary in Figure 855 is adapted from Smith's work.

Howard (1950) obtained complete clinical and serologic cure in 45 per cent of his cases with forty-nine weeks of treatment.

Significance of Fixed Positive Serologic Test.—Cole *et al* (Cooperative Clinical Group, 1937) found that a fixed positive serologic reaction in patient with late prenatal syphilis while he had acute lesions, or residual evidence of previous activity does not justify so good a prognosis as though the blood serologic test had reversed to negative. In the latent congenital syphilitic, it does not appear that serologic fastness influences clinical progression or relapse. The Cooperative Clinical Group studies with late prenatal syphilis showed that the amount of treatment did not appear to affect the reversal of the serologic reaction of the blood. More than half had fixed

Fig. 855

RESULTS OF TREATMENT OF CONGENITAL SYPHILIS
(After F R. Smith, Jr)

Age at commencement of therapy	Percentage cases. Seroresistant.	Showing clinical relapse.	Showing satisfactory clinical outcome.
1. Birth to 3 months	17 9	6 4	} 95 3
2. 4 to 6 months	26 1	10 9	
3. 7 to 12 months	27 3	15 1	
4. 13 to 24 months	38 3	19 4	
5. 2 to 4 years	41 3	4 4	93 7
6. 5 to 7 years	78 5	7 8	86 4
7 8 to 10 years	80 1	3 6	87 5
8. 11 to 15 years	86 2	8 5	91 5

positive serologic reactions despite treatment given. Howard (1950) also feels that positive blood serologic test after adequate therapy in the absence of other clinical signs is not of unfavorable prognostic import. Forty per cent of 45 children observed by him over ten-year period remained seropositive.

Special Problems—Interstitial Keratitis.—*Interstitial keratitis* should never be managed without the cooperation of the ophthalmologist. The delegation of the instillation of atrópine, so essential a part of local treatment to the parent does not appear to be satisfactory and iritis with synechia may result. Hot fomentations formerly much used seem less essential now Dionin is of distinct service. Salicylates internally are of some value in controlling pain and the secondary uveal involvement (Woods, 1943) The child must discontinue school and the eyes must be protected with tinted glasses. The tendency of children in this condition to sequester themselves indoors must be tactfully dealt with and every possible means taken to maintain the general health and morale

Adequate early treatment of congenital syphilis prevents the development of interstitial keratitis. Cole *et al.* (CCG) 1937 found that only 2 per cent of patients who received modern antisyphilitic treatment developed interstitial keratitis, whereas 90 per cent of patients who developed interstitial

keratitis had had no previous treatment. Effective systemic treatment has a rapidly favorable effect on the course of interstitial keratitis. In particular the effective use of arsphenamine will, in conjunction with a soluble mercurial salt intramuscularly used simultaneously bring surprising relief from photophobia and discomfort in four or five weeks This Stokes believes to be definitely superior at least to insoluble bismuth. The course of quite severe cases can be reduced from the usual period of six to eighteen months to from two to six months the rate of clearing of the cornea seeming less affected than the acute phase DeSchweinitz found arsphenamine in 0 4-Gm. doses most valuable Klauder and Vandoren (1941) have shown that contrary to previous practice, there is no justification for the customary use of iodides, either orally or intravenously in active or inactive interstitial keratitis. Careful analysis indicates that iodides may even be harmful It should be recalled that the use of small doses of neoarsphenamine at biweekly intervals without simultaneous mercurialization, which seems to be common practice is not regarded in this discussion as efficient treatment. Nonspecific methods may be invoked including especially because of its convenience boiled milk injections, 2 to 10 cc in older subjects for a series of 8 to 10 injections.

The results of our methods of treatment in a small number of cases which it was possible to completely recheck over a period of several years are given in Figure 85" to be compared with the better results of fever and chemotherapy (Klauder and Vandoren) Many of our patients came to us with chronic relapsing cases in which a high degree of opacity and vascularization already existed Had we been able to apply at the outset in all cases the treatment methods above outlined we feel confident that a shorter course and fewer residua would have been the rule. In patients seen within the first two or three weeks residual opacity and vascularization can often be absolutely prevented.

The attack of interstitial keratitis should be treated to an absolute standstill and no signs of activity should be detectable by the ophthalmologist before the patient is placed on any prolonged rest interval In patients who have a high degree of opacity and vascularization, measurable degrees of improvement can be obtained by the persistent use of arsphenamine and heavy metal over several years

Klauder and Vandoren (1941) found that chemotherapy was of limited value in improving visual acuity in inactive interstitial keratitis, less than 5 per cent of 115 eyes being benefited While both the Cooperative Clinical Group and Klauder's studies show that excellent results are obtained with the early use of chemother py in active interstitial keratitis, the latter studies also show that relapse is much better prevented [illegible]hen chemotherapy is supplemented by fever therapy Chemotherapy should consist of not less than twenty [illegible] eeks of arsenical with interim heavy metal When this treatment is continuous and commenced within t[illegible] months after onset between [illegible] per cent and 80 per cent satisfactory results can be obtained but relapse occurs in between [illegible] per cent and 18 per cent of cases. Routine therapy supplemented by fever therapy in [illegible] patients treated by Klauder resulted in only one relapse (1.8 per cent) and this patient had received only 2 injections of typhoid vaccine Visual acuity was best after the use of malaria, while typhoid vaccine produced less satisfactory results, and boiled milk was least effective

Woods (1943) discusses the value of roentgen irradiation in causing resolution of the infiltrate on the cornea, but points out there is a definite danger of damage to the lens and late effect, particularly if the roentgen ray is used. Theoretically of equal value [illegible]ith the roentgen ray and of comparativ[illegible] safet[illegible] is irradiation with the beta rays of radium. These penetrate only [illegible] or 2 mm. and do not reach the lens. They are given just short of contact and [illegible] total of about [illegible] gram 40 seconds in divided doses over [illegible] six week period, constitutes a full course. Each [illegible] infiltration of the cornea is followed by clearing of the infiltrates and irradiation has an inhibitory

effect on such vascularization, it is probably wisest to postpone any phototherapy until vascularization is fairly well established.

Deafness.—The heredosyphilitic child who has once developed a complete eighth nerve deafness does not respond in any appreciable degree to treatment as does the patient whose deafness is associated with an acquired neurosyphilis. The occasional premonitory tinnitus in childhood which

Fig. 836.

FEVER AND CHEMOTHERAPY RESULTS IN INTERSTITIAL KERATITIS
(After Klauder and Vandoren.)

Mode of therapy	Visual acuity 20–40 or better per cent.
Malaria	75
Hyperthermia	72
Typhoid or antigen H	50
Boiled milk	43

terminates in deafness at puberty should be more often the clue to diagnosis and treatment.

Neurosyphilis.—The prognosis of neurosyphilis, particularly if recognized in the asymptomatic stage, is better in the child than in the adult. Clausen and Jeans remark that the earlier a child with neurosyphilis is treated, the better the outlook and the quicker the desired result is obtained. They find this observation in keeping with the much larger amount of arsenic found in the spinal fluid of infants than older children, and the clinical fact that intraspinal therapy is rarely necessary in dealing with infantile neurosyphilis.

TREATMENT RESULTS IN 50 CASES OF INTERSTITIAL KERATITIS

	Cases	Per cent.
Improved	21	42
Arrested or unchanged	12	24
Improvement uncertain	9	18
Worse	8	16
Total favorable results		66
Doubtful or unfavorable		54

Fig. 837

Juvenile paresis is yielding to modern methods, though opinion is still in the making, and its high resistance is recognized. Its treatment is essentially the same as in the adult. Moore endorses malaria (1043) emphasizing its use before deterioration sets in, and the risks of tryparsamide. Tabes with crises or optic atrophy is as unmanageable as in the adult. In Potter's (1933) report on 38 cases, malaria and tryparsamide arrested 27 with complete remission in 5 partial in 0 cases, observed two to nine years. Potter found the prognosis better in patients normal before the onset of dementia who were past adolescence at onset who showed expansive and confused types of reaction or

whose paresis had not been of longer duration than two years. Menninger's (1936) monograph gives an excellent summary of this subject. In general therapy is similar to that which has been described for the adult (q.v.). Malaria is ordinarily the fever therapy of choice; tryparsamide is normally contraindicated unless visual acuity can be determined because of the danger of optic atrophy.

Asymptomatic Patient with Positive Blood Serologic Test.—The management of the patient whose only presenting symptom is a positive blood serologic test and whose spinal fluid examination is negative will depend largely upon the age of the patient. To be certain that the infection is congenital and not acquired, some definite stigma of the disease must be present in the absence of definite knowledge that the infection was present in early infancy. If such information is not available, then the patient should be considered to have acquired syphilis and be treated for such, irrespective of his age. Especially to be cautioned against, is the practice, still prevalent, of making a diagnosis of congenital syphilis, in a child or young adult, merely because no satisfactory history of the symptoms of acquired syphilis can be elicited.

If the diagnosis of congenital syphilis is established, and the patient is less than twenty-five years of age, then minimum standard treatment to prevent interstitial keratitis should be given: sixteen weeks arsenical and thirty weeks heavy metal therapy. The likelihood of any serious late manifestation of congenital syphilis appearing after this age is reached makes further therapy inadvisable and it is questionable whether anything more than periodic observation is needed should the congenital syphilitic be over twenty-five years of age when first seen.

The Well Child in a Syphilitic Family.—The child who, though of syphilitic parentage, has a negative blood and spinal fluid, and no stigmas of the disease detectable by complete physical, ophthalmoscopic, and aural examination, is hardly in need of treatment. (See previous section on indications for treatment.)

The Marriage of the Heredosyphilitic Adult.—The victims of severe heredosyphilitic manifestations are probably best advised not to marry since there is still ground for fearing that they may impart abnormal diathesis to their offspring. On the other hand, the usual patient with a few stigmas, a positive serologic test, and perhaps an interstitial keratitis from which he makes a good recovery under effective treatment, is not ineligible for marriage. Sidler-Huguenin, who studied this question in the children of 250 persons whom he knew to have heredosyphilis, found that 28 per cent of the families were childless and the life expectancy was somewhat shortened, but that the children were normal and that there were no apparent drawbacks, other than those mentioned, to the marriage of those who have inherited syphilis. Hufer and Wiskott compared 40 patients with prenatal syphilis with controls, with reference to their descendants, and found no difference between the two groups in the incidence of abnormality or pathologic change. (See previous section on third generation syphilis.)

The Welander School-homes for Heredosyphilitic Children.—In dealing with the heredosyphilitic child, and especially the orphan or illegitimate, often bright and precocious but handicapped by some special disability or complication which demands expert attention over a period of years, one is impressed with the real worth of the plan developed by the Scandinavian syphilologist, Welander, for the raising of these children in school-hospitals

or homes in which the adequate treatment of their condition, demanding as it does unusual persistence, can be combined with formal education and healthful surroundings. Since the first home was opened by Welander through private generosity at Stockholm in 1900, with 4 children, the idea has extended into Norway and Germany and the original establishment has been greatly enlarged. The reported results (Balze, Müller and Singer Rondet) of this form of management for children who cannot have adequate home care are superior to any plan thus far devised and deserve consideration by child welfare authorities and agencies in this country

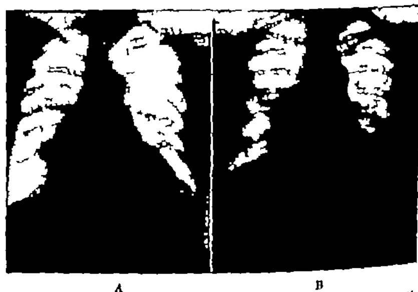
CHAPTER XXII

MISCELLANEOUS ASPECTS AND CASE MEMORANDA

The following brief summaries deal with relatively less common manifestations of syphilis to which restricted space is given in order to keep the foregoing material within the compass of single volume.

SYPHILIS OF THE LUNG AND MEDIASTINUM

Pulmonary Syphilis.—Syphilis of the lung has been admirably reviewed in extenso, with a summary of the literature, by Carrera, Wile and Marshall, McIntyre, and Levin. Acquired syphilis of the lung is regarded as rare, and seldom demonstrated short of the necropsy table. Pulmonary involvement in the form of interstitial pneumonitis is, of course, common feature of heredosyphilis. Of the acquired form Osler recognized 12 cases in 2500 necropsies. Carrera in Warthin laboratory found 12 cases among 152 necropsies of known syphilitic persons.



A B

Fig 838.—A, Syphilis of the right lung. Insofar as there is typical picture, this is it. Note the response to treatment in B (Courtesy of Drs. Stroud, Bowen and Bishop.)

Three important papers, those of Pearson and DeNavasquez (1936), Ha, Fraser and Hsieh (1939) and Levin (1940) bring the subject up to date. It must be conceded that differential diagnosis short of topsy and tissue examination appears more and more rather than less and less difficult.

Clinical pulmonary syphilis of the acquired form consists of solitary gumma, diffuse syphilitic fibrosis, and possibly diffuse syphilitic bronchopneumonia. Secondary involvement of the pleura may give rise to true syphilitic pleuritis. The boundary line between syphilitic involvement of the hilus of the lung and syphilitic mediastinitis is, of course, impossible to define in some cases.

Head and Seabloom have directed attention to pulmonary complication of syphilis associated with acute lobar pneumonia in report of 5 cases of delayed resolution, the fever and pulmonary symptoms persisting for days or weeks and giving the impression of interlobar pleurisy or empyema. The blood serologic reactions were positive the symptoms disappeared rapidly following the administration of arsphenamine. Subsequent to the above report, Farrell, Stanley Floyd, and Fitzhugh have discussed the subject, the last mentioned author reporting

3 cases. In case presented by FitzHugh and Anderson before the College of Physicians of Philadelphia massive infiltration of the right upper lobe had occurred with gumma of the right base. The symptoms disappeared rapidly following the use of mercurial inunctions and sodium iodide by mouth. While it cannot be said that syphilis is the first factor to be considered in interpreting unresolved pneumonia even in syphilitic subjects, it seems probable that the condition is more frequent than is generally recognized and that the presence of positive blood Wassermann test in patient with unresolved pneumonia should lead to treatment with mercury bismuth, and iodide before operative measures are considered. Even relapsing pleurisy with effusion may pparently occur in such cases and respond to treatment for syphilis.

Fig. 859

THE DIFFERENTIAL DIAGNOSIS OF ACQUIRED PULMONARY SYPHILIS AND TUBERCULOSIS

Syphilis	T berculosis
Concomitant evidence of syphilis.	N concomitant vidence.
Sputum repeatedly negative for tubercle bacilli (*Spirochaeta pallida* also not demonstrable)	Positive sputum.
Delayed resolution of lobar pneumonia in patient with syphilis.	
Right side most frequently affected.	Left side most frequently affected.
Lower or middle lobe involvement most frequent. "Pathologic changes in right lower lobe strongly suggest syphilis (Karshner and Karshner)	Apical involvement most frequent.
Pathology	
Spirochetes demonstrable (Warthin).	
Caseation not so marked.	Caseation more marked.
Blood vessels only occasionally ttacked.	Blood vessels often ttacked.
Anthracosis infrequent.	Anthracosis more frequent.
No epithelioid formation.	Epithelioid formation.
More pleural connective tissue scarring.	Less pleural connective tissue scarring.
Peripheral (subpleural) lesions common.	Peripheral lesions not the rule.
-Ray	
Calcification not common.	Calcification common.
Cavitation rare.	Cavitation common.
Gumma sharply circumscribed.	Margins of lesions more hazy
Lower and middle lobe shadows.	Apical shadows.
Fibrous tracts radiating from main lesion.	
Occasional polycyclic shadows.	
Often marked peribronchial sclerosis.	
Response to specific therapy excellent in pulmonary gumma, good in interstitial pulmonary syphilis if not too advanced.	Occasional nonspecific response to arsphenamine.

Much of the material on which this table is based is contained in McIntyre' article, and Levin in the Jadassohn Handbuch.

It is an interesting question whether pulmonary spirochetal crisis such as may occur in the brain in paresis or the heart muscle in acute syphilitic myocardial failure (Warthin), may not give rise to the clinical picture of acute pneumonia with delayed resolution.

The clinical symptomatology of chronic syphilis of the lung is nonspecific. In no case can a diagnosis be made without collateral evidence of syphilis, and autopsy or successful therapeutic test, carefully guarded against nonspecific misinterpretations. Gumma of the lung may pass for neoplasm, softened gumma for pulmonary tuberculosis with cavitation, and interstitial pneumonitis for nontuberculous lung infection, and even pulmonary fibrosis such as pneumonoconiosis.

The crux of the clinical undemonstrability of pulmonary syphilis lies in its masquerade as tuberculosis. It has been surprising feature of our personal experience to note the frequency of report of "healed apical tuberculosis" in association with active late manifestations of syphilis in th upper respiratory tract and the nasopharynx. From such cases we have derived the impression that pulmonary syphilis is perhaps clinically obscure, but not excessively rare.

The touchstone in diagnosis is the collateral evidence of syphilis, before mentioned, and the *repeated absence of tubercle bacilli in the sputum* over a considerable period, in cases whose clinical findings and roentgenograms suggest an open type. Fever, productive cough, bloodstreaked sputum, gastro-intestinal symptoms, weight loss, and even night-sweats are not impossible in pulmonary syphilis uncomplicated by active tuberculosis. Therapeutic tests should be performed with mercury or bismuth. Arsphenamine and iodide have too large margin of nonspecificity for safe interpretation.

Gumma of the trachea and of the bronchi (often diagnosed gumma of the lung) is quite rare and usually recognized late. It may be associated with gummatous involvement of the larynx. Inspiratory stridor and dyspnea with a dry brassy cough and paroxysmal attacks suggesting



Fig. 860.—Characteristic posture of the patient with mediastinitis producing venous and lymphatic stasis in the neck and arms. The crowding upward of the tissues in the supraclavicular fossae, with the thickening and edema, produces an apparent shortening of the neck and a frog-like forward thrusting of head and arms. There are numerous large *superficial* veins over the presternal region (obstruction of the superior vena cava) The eruption is tinea versicolor

asthma are common symptoms There may be scanty blood-tinged sputum. Roentgenography bronchoscopy examination of the sputum, and collateral evidence of syphilis with therapeutic test are essential to diagnosis. Bronchiectasis may follow upon or be associated ith the deeper lesions.

Asthmatic syndromes ascribed to syphilis, the diagnosis based almost entirely on therapeutic tests, are discussed by Mayer and Mossolin (1937) with summary of the literature.

Ayerza's Disease.—I 1901 Ayerza described disease complex in hich the pathologic changes consisted of chronic bronchitis, bronchiectasis, emphysema, and stenosis and obliteration of the pulmonary vessels. The pulmonary disturbances result in compensatory enlargement of the right heart and an erythrocytosis of degree approximating t times that seen in polycythemia rubra vera, with which the complex is sometimes confused. Herxheimer states that

cases in which the luetic nature of the arterial changes can be accepted have been reported by Warthin, and by Escudero, the latter stating that most cases are syphilitic. Herxheimer believes, however that the variable complex of Ayerza disease probably is dependent on number of factors including lues, malaria and chronic intoxications, and that the etiologic agent may be difficult to uncover in given case.

Syphilitic Mediastinitis.—Syphilis of th mediastinum has been presented and discussed to some extent in connection with cardiovascular syphilis (see especially case reports. Chapter XIX) Giffin summarized the situation on the basis of 5 ases seen t the Mayo Clinic, and Lemon discusses in full the differentiation of mediastinal affections.



Fig 861.—Thickening of the neck and venous compensatory circulation in patient recover ing from an extreme *grade of gummatous mediastinitis, with obstruction of both superior and* inferior vena cava

An uncomplicated mediastinitis is diagnosed with comparative ease when sufficiently severe to be responsible for marked pressure symptoms or to cause well-defined roentgenographic shadow The abortive forms, however, may give rise to no more than retrosternal pressure and slight pain, glottic spasm, hoarseness, fulness of the neck, and slight changes in the collateral circulation. A well-marked case of middle mediastinal infiltration presents striking picture. The edema of the neck, venous engorgement, swelling of the arms and tracery of vessels over the thorax, the bulging eyes and slight stoop with arms thrown forward akimbo, suggesting the attitude and appearance of frog, are recognizable on sight (Fig. 860) The possible extent of the mediastinal changes and the involvement of surrounding structures are illustrated in Fig 862. If the inferior vena cava be subject to compression in the process the symptoms may be suggestive of hepatic cirrhosis and the collateral circulation (Fig. 861) involve the superficial abdominal

Fig 308.

PULMONARY MALIGNANCY VERSUS PULMONARY SYPHILIS

Housewife, aged thirty-eight.

Examined 9/18/22.

Chief Complaint Hoarseness and pain in whole left chest and shoulder

No difficulty in swallowing, no dyspnea, no orthopnea.

Weight Loss 100 pounds in eighteen months.

Pain Requires Morphia.

Has Had a Diagnosis of Pulmonary Malignancy and Several Massive x-Ray Treatments Given Some Months Ago. No relief.

Wassermann Elsewhere Reported negative.

Examination

Clubbed fingers marked.

Exophthalmos slight

Left pupil slightly the larger

Enlarged veins left upper chest.

Restricted breathing

Blood-pressure same both arms. 180/70.

Breath sounds and voice decreased over entire upper half left thorax both front and back.

N pulsation, no diastolic shock, no tracheal tug

Temperature normal.

Heart negative

Liver and spleen palpable.

Leukocytes 23 400 Hemoglobin 80 Differential count 87 per cent. polymorphonuclears.

Blood Wassermann Reaction: Strong positive repeatedly

x-Ray of Chest: "Marked increased density over hole upper left lobe. Probably tumor Area over right diaphragm probably metastasis.

Re-ray Three Days Later: No change.

Left Vocal Cord in Midline.

"May be Necrosis in Tumor—Note Leukocytosis.

Clinical and Surgical Diagnosis: Malignant tumor left chest with metastasis on right.

Referred to Syphilologist: Unable to stay for treatment. Given forty 30-grain inunctions and potassium iodid, to take home.

One Month Later Reports She is Feeling Easier in Chest and Voice is Better.

Five Months Later Reports Cough is gone, has gotten her voice back and everybody who sees her says she "looks good.

One Year Later: Letter from home physician states patient died suddenly ith symptoms very suggestive of ruptured aneurysm.

Necropsy refused.

DISCUSSION

1 This patient well illustrates the problems that syphilis of the lung or malignancy may present. A negative Wassermann elsewhere, two positives in the clinic, afebrile but with leukocytosis, signs of pressure and mediastinitis, but no signs of aneurysm, and an extreme loss of weight ith lesions in both lungs. N response to x-ray therapy

2 It is rule worth bearing in mind that when malignancy or suspected malignancy presents anywhere in operable form, operate. But inoperable malignancy in situation such as the thorax deserves therapeutic test for syphilis with mercury and iodid. It is matter for debate whether x-ray therapy is entitled to precedence over syphilotherapy here or not unless the diagnosis of malignancy is borne out by absence of signs of syphilis, and, if possible, positive gland findings for malignancy

3. N suspected inoperable malignancy with positive blood Wassermann should escape having therapeutic test for syphilis. She had had negative test elsewhere

4 It is quite conceivable that pulmonary gummatous syphilis may be bilateral.

5. Softening may occur in a gumma in any location.

6. Weight loss does not make diagnosis of malignancy or speak against syphilis. Constant pain alone, irrespective of syphilis, can lead to marked weight loss from insomnia, etc and is common observation in aneurysm.

7 Note the clubbed fingers, of course not suggestive of syphilis.

8. The diagnosis on this case was by no means settled by the temporary outcome. It was entirely possible that she still had malignant process complicated by syphilis with partial relief

9 The suggestion of aneurysm contained in the physician death report was a complete surprise, and, while not established by necropsy, suggests the care which must be used in diagnosing non-pulsating masses in the middle chest ithout providing for therapeutic test for syphilis.

Fig. 863.

SYPHILITIC MEDIASTINOPERICARDITIS AND PNEUMONITIS; RECOVERY UNDER TREATMENT FOR SYPHILIS. COINCIDENT NEUROSYPHILIS

Housewife, aged fifty-two.

Examined 12/30/21

Chief Complaint: Cough and swollen fingers. One and half year duration, occasional bloody sputum, violent paroxysms of coughing. Dyspnea, orthopnea.

Fingers Clubbing for Past Three Months.

Attacks of Dizziness, girdle sensation, some taxia, paresthesias, etc., referable to the neurosyphilis.

Examination

Demonstrable neurosyphilis (pupils, etc.)

Deep dulness left base increased breath sounds, and whispered voice.

Click over apex of heart in fourth interspace. Otherwise negative.

Fingers markedly clubbed, pink color

N cyanosis on stooping

x-Ray of chest negative except heart enlarged and drawn to left.

Electrocardiogram left ventricular preponderance.

Sputum Examinations (three) negative for tubercle bacilli.

Blood Wassermann Reaction Strongly positive.

Spinal Fluid Strongly positive.

Consultant's Diagnosis Findings chiefly those of pleural thickening (involving pericardium?), but with dyspnea, chronic cough, bloody sputum, and clubbed fingers, should mean tumor or mass in chest.

Treatment for Syphilis Begun: Twenty injections mercury succinimid, sodium iodid by mouth.

Bronchoscopy Negative.

N Palpable Glands, neck or axilla.

Apical Retraction Noted, but no Broadbent sign.

T and Pre Apical Murmur (rub?)

Consultants Disagree to Whether Signs Justify Diagnosis of Adherent Pericardium.

By Tenth Day of Treatment marked improvement in all signs.

Fourteenth Day (mercury and iodid only) Cough gone, pain in side gone, fingers much smaller, general gain.

Neo-arsphenamin Begun Mercury continued. Further improvement.

Consultants Still Differ as to Cardiovascular Disease.

Neurosyphilis Resistant to Ordinary Treatment.

Patient Sent Home after 6 neo-arsphenamin, 5 intraspinal, 26 succinimid, 24 sodium iodid injections.

Heart Negative, Fingers Much Smaller Some Râles Both Bases, N More Apical Retraction.

Returns in Excellent Health for Observation N signs of pericarditis, heart negative as to physical signs, but -ray plate still shows enlargement and drawing to left. Symptoms gone entirely Will not remain for full course of treatment.

DISCUSSION

1. In retrospect while the diagnosis of this case remains undetermined, strong presumption of syphilitic pneumonitis nd pericarditis seems to exist.

2. The possibility of non-syphilitic lung infection forming the basis upon which the syphilitic lesion developed must be considered.

3. The therapeutic test as carried out as as nearly non-specific as possible. No arsphenamin was used to confuse the issue with pulmonary spirochetosis or non-tuberculous lung infection such as has been seen since the epidemics of influenza.

4. Blood-streaked sputum and slight fever are entirely compatible with syphilitic pneumonitis.

5. There was no sign of localized mass, which would t once have raised the possibility of malignancy though it might have been gumma.

6. Note that the clubbed fingers improved with the response of the pericardium and lung to treatment for syphilis. There were no -ray or clinical signs of periostitis or ostitis.

7 The Wassermann test and the finding of neurosyphilis really forced this diagnosis to the point of therapeutic test. More frequent use of non-specific therapeutic test in pulmonary lesions having repeatedly negative sputum examinations for tubercle bacilli and pulmonary spirochetes, would perhaps increase the prevailing estimates of the importance of pulmonary syphilis.

8. Arsphenamin has marked effect on variety of non-syphilitic lesions of the lung, and cannot be trusted for therapeutic tests.

as well as the thoracic veins. The most striking symptom in severe grades of syphilitic mediastinitis which Stokes has seen is the pronounced cyanosis which develops on stooping or lying down, as evidence of venous obstruction, of course, not specific for syphilis. It is not, however, invariably present.

Figure 863 illustrates the symptomatology of a probably syphilitic mediastinopericarditis, and the nonspecificity or rather lack of differential value of many of the symptoms commonly accepted as almost pathognomonic of aneurysm and other causes of mediastinal pressure. Figure 862, on the other hand with mass in the lung and a mediastinal shadow as regarded as malignant because of the coincident presence of the mediastinal shadow and the mass in the lung. The patient improved greatly under treatment for syphilis, and then abruptly died with symptoms practically conclusive of aneurysm. Tuberculous mediastinitis has twice been referred with anomalous Wassermann findings (weak positives) for therapeutic test. In one of the patients the abscess rapidly came to head and perforated the sternum during the latter part of six-week course of arsphenamine treatment. In the other case no significant improvement was obtained, and the case was regarded as tuberculous by inference.

The diagnosis of mediastinal syphilis would indeed be easy if it could be based merely upon a mass, a definitely positive blood Wassermann reaction, and positive therapeutic test. It is malignancy with coincident syphilis, syphilis and pulmonary gummas simulating malignancy with coincident syphilis, and solid mediastinal masses with negative blood serologic reactions which develop pulsation on therapeutic test for syphilis and become indubitable aneurysms, that



Fig. 864.—Clubbing of the fingers in syphilitic mediastinopericarditis and pneumonitis (Fig. 863) The clubbing disappeared as the mediastinal and pulmonary process involuted under treatment. There were no signs of osseous changes clinically or roentgenographically.

torment the diagnostician. In the presence of collateral evidence of syphilis and signs of mediastinal mass, then, the safest general rule is to approach the case as one of vascular syphilis, not because it is such necessarily but because such procedure gives the lowest percentage of temporary nonspecific results, if the process is tuberculosis or Hodgkin disease, and the greatest safety t the patient if the mediastinitis resolves itself into aneurysm.

GUMMA OF THE LYMPH NODES

This condition, pitfall for the unwary internist and surgeon, while not common, has not been rare in our experience. Hazen states that gumma of the lymph nodes is comparatively common in the colored race. Laymon (1934) and Herbert Fox (1936) have discussed the histologic differentiation of gumma of the lymph nodes in biopsy diagnosis, and the former found 15 per cent of 70 patients with early syphilis to present "tuberculoid" reaction in the lymph nodes, mostly inguinal. In the cervical region (Figs. 865–867) the only safeguard against error and unnecessary operation for tuberculous glands may be the routine use of the blood serologic test. Gummatous lymphadenopathy or at least local syphilitic lymphadenopathy may help to confuse diagnosis in aneurysm with mediastinitis (Chapter XIX), may produce clinical appearance of malignancy in association with abdominal lesions, including the stomach, the gallbladder and the rectum (Chapter XVII), and of the axillary lymph nodes (gumma of the breast). On the other hand, in the inguinal region Stokes has seen an inguinal adenitis due to Hodgkin disease submitted as *ipso facto* due to syphilis even though the blood serologic reaction and collateral findings were negative. Errors of the kinds described can be dealt with in only one way—by diagnosis to consider syphilis as possible complete explanation of an apparently nonspecific abnormality and by the thorough study of each and every case. Those who rely on these diagnoses exclusively



Fig. 865.—Gumma of the cervical lymph nodes mistaken for tuberculous lymphadenitis and twice apparently operated upon as such, with recurrence. The entire right side of the neck and the tissues posterior to the ramus of the jaw and over the parotid were brawny and indurated Following the finding of positive blood Wassermann reaction the entire process disappeared under treatment for syphilis. This patient oldest child had bilaterally symmetric hydrarthrosis of the knees (see Fig. 866)

for their opinion of an adenitis will make as serious mistakes as those who rely solely upon a blood serologic reaction.

LATE SYPHILIS OF THE KIDNEY URETER, AND BLADDER

Syphilis of the Kidney Ureter, and Bladder.—The kidneys of large proportion of syphilitic patients are found at necropsy to be abnormal in one way or another, especially with reference to chronic inflammatory change. The precise relation to syphilis is difficult to establish. Rich describes peculiar form of nephritis encountered in 9 per cent of 200 necropsies in which there was definite pathologic or serological evidence of acquired syphilis. I control series of 400 cases the lesion was never found in the absence of syphilis. The possible damage that may occur in the kidney during the stage of spirochetemia seems not to be appreciated fully Warthin has demonstrated numerous spirochetes in the tubular and epithelial tissues of the kidney in 5 cases of acute syphilis, 2 acquired and 3 congenital in origin Hermann states that trace of albumin or occasionally red blood cells may be found in almost 8 per cent of patients with spirochetemia. Miller and Hay have reported case of what may be classified as nephrorecurrence or renal spirochetal crisis. In their patient syphilis had been latent for some twenty years when evidence of an acute nephritis developed and death rapidly ensued. At necropsy the kidneys presented the picture of chronic nephritis on which an acute process had been superimposed affecting all the structures of the organ. Spirochetes were readily demonstrable in the tubules. Riviere believes that syphilis is sometimes the cause of albuminuria in pregnant women on the basis of his finding syphilis in only 8 per cent of women without albuminuria, while 23 per cent of the cases with albuminuria showed positive Wassermann reactions. From review of the literature and their own experience, Miller and Hay believe that syphilis of the kidney may be satisfactorily classified as follows:

I. Nephritis of the early stages (spirochetemia)
   (a) Acute glomerular nephritis, rare form characterized by low albumin content and numerous blood cells in the sediment (Hein, Zentral. f. inn. Med., 10 263, 1927).
   (b) Acute tubular or parenchymatous nephritis of which the lipoid nephrosis of Munk (Ztschr f. klin. Med., 78 1913) is type, characterized by very large amount of albumin, by hyaline granular and fatty casts with but few red blood cells. Most of the cases of acute syphilitic nephritis fall in this group.

Fig. 880

INTERPRETATION OF A SUPPURATIVE ADENITIS WITH A POSITIVE WASSERMANN REACTION

Male, aged nineteen, single.

Chief Complaint: Draining glands in the neck, enlarged glands in inguinal and axillary regions.
Father and mother dead, details unknown.
Six years of trouble with glands.
Cleared up temporarily by tuberculin (?)
Glands in the involved regions recurred and subsided t intervals up to one year ago, then marked recurrence in neck.
Tonsillectomy four years ago
Surgical removal glands right neck one year ago. Draining since through sinus.
Gonorrhea one year ago.
No history of Lues I or II
Chest negative. No T.B symptoms. No fever
SWR strong positive followed by negative.
Syphilologic Examination: N signs of acquired or inherited syphilis. Never been treated for syphilis that he knows. Provocative yielded negative, +++ +++ negative, negative, negative
Eye negative. Spinal fluid negative.
Neurologic Examination: Negative except slight nystagmus.
Full examination for tuberculosis negative except for glands (none excised).
Treatment: Six injections arsphenamin, 20 inunctions.
Four x-ray exposures coincidently ordered by another consultant.
BWR +++ after treatment
BWR negative after 60 more inunctions
Second arsphenamin course Six injections.
BWR negative, direct and provocative for two years.
No further treatment.
Spinal fluid negative.
Glands reduced 80 per cent., still palpable; sinus healed.

DISCUSSION

1 The patient is young for an acquired infection. If acquired with the gonorrhea ithout treatment, the BWR without treatment should be unconditionally positive

2. The cervical glandular enlargement which was operated on might have been the bubo of tonsillar lues I. This is unlikely in the absence of history of sore throat and ithout frank positive BWR.

3. If a childhood infection, the condition would be a gumma of the lymph-nodes This is usually localized to single group of glands and follow contributory cause such septic infection, i tonsillitis in the area of lymphatic drainage. Tuberculosis is more likely to invol several groups. Sinuses favor tuberculosis, but may be present ith gummas. They do not accord ith operated bubo of lues I.

4. Patients with tuberculosis may give false positive Wassermann reactions. These are usually partial positives (+ ++) They are pt to ppear ith little reference to treatment.

5. This patient may have had false provocative effect.

6. The therapeutic test with arsphenamin on gland masses is untrustworthy Tuberculous glands will often respond.

7 Th therapeutic test here was further vitiated by the us of -ray by another clinician. This alone might ha cured the glands, though seldom so promptly or with so few exposures as in this case

8. Great care in therapeutic tests must be used to avoid ( ) non-specific effects; (b) multiple procedures ith consequent inability to decide later hat did the work.

9. This boy must remain under observation indefinitely with an undetermined condition, probabl tuberculous.

10. A pathologic examination of an excised gland should have been made but would not have been absolutely conclusive. Animal inoculation could be used.

II. Nephritis of the later stages.
( ) Secondary syphilitic contracted kidney
(1) Chronic glomerulonephritis (Fordyce Miller and H y).
(2) Chronic interstitial nephritis, the end-stage of lipoid nephrosis (Munk)
(b) Chronic parenchymatous nephritis, syphilitic type of large pale kidney (Fournier) intermedi t stage of lipoid nephrosis.
( ) Chronic interstitial nephritis associated with vascular disease
(d) Amyloid kidney (?)

III Kidney of congenital syphilis.

Fig. 367

GUMMA OF THE LYMPH NODES, CONFUSION OF TUBERCULOSIS AND SYPHILIS. EFFECT OF ARSPHENAMIN ON OPTIC ATROPHY

A woman with a mass suggesting matted glands below the right jaw. Sinuses with ulceration.
Glands enlarged after tonsillitis.
The Scars of Two Operations for Tuberculous (?) Glands.
An arciform ulcerative lesion along the border of one of the scars.
Divorced six months after first marriage to "brute.
SWR Strongly Positive.
High myopia with primary optic atrophy.
CSF WR negative; Nonne negative; 8 lymphocytes.
Bárány positive.
No neurologic findings.
Treatment. Five injections arsphenamin, 3 to 4 decigrams.
No Herxheimer reaction.
Slow improvement.
Eyes Grew Rapidly Worse During the Course. Sixth Injection Omitted.
Lesion only partly healed when discharged, but healed completely while home on 40 injections.
Another Arsphenamin Injection Four Months Later Made the Eyes Markedly Worse ("Like a Cloud").
Fundus examination: Optic atrophy is progressing.
Patient can tolerate 1- to 2-decigram doses of arsphenamin fairly well. Eyes stationary under mercury.

Discussion

1. If the surgeon had noted the marital history and taken a Wassermann test the patient might have been spared two unsuccessful operations.

2. Gumma of the lymph nodes may come on after tonsillitis precisely as in the case of tuberculous glands.

3. The bubo of a tonsillar chancre does not break down.

4. False positive Wassermann results (usually one or two plus) may occur with tuberculous glands.

5. Tuberculous glands with sinuses may heal under arsphenamin, even in the absence of syphilis—a false positive therapeutic test.

6. The pathologic differentiation of gumma and tuberculoma is not always trustworthy.

7. The prominence of the cutaneous as compared with the glandular lesion, the repeated positive Wassermann over a period of months with final reversal under treatment, the slightly abnormal spinal fluid and the positive Bárány (inflammatory process in the brain stem) all speak for syphilis.

It may be impossible to make a differential diagnosis between syphilis and tuberculosis in certain cases without prolonged observation. Look for a tubercle bacillus.

Primary optic atrophy from whatever cause, may sometimes respond unfavorably to arsphenamin.

Stengel and Austin noted the presence of a double-refracting lipoid (Fig. 401) in a larger proportion of cases of nephritis associated with positive Wassermann reactions, than in nonsyphilitic patients. Paroxysmal hemoglobinuria is described in Chapter XXI.

Two reviews, those of Hermann and Marr (1935) and Baker (1939) have emphasized the need for a massive study of syphilis of the kidney with fuller case data, but without contributing anything radically new to the foregoing résumé.

Gumma of the kidney is a rarity although undoubted cases are on record (cf. for example Hunter, 1939). It may be suspected in patients who, in conjunction with a late syphilitic infection, develop a sudden hemorrhage with much detritus in the urine. Syphilitic pyelitis has been reported, but convincing proof of its syphilitic etiology is lacking. A proved case of syphilis of the ureter is not on record.

Posner states that 100 cases of syphilis of the bladder are found in the literature but objects to the sole criterion of therapeutic response as the evidence in many of these. Early syphilis of the bladder is exceedingly rare and takes the form of macular, papular and ulcerative lesions coincident with the secondary exanthem on the skin. Jovanovitch states that involvement is most marked in the more vascular regions of the trigone and fundus, and that the lesions are always submucosal and never ulcerative at the onset. Late syphilis of the bladder is usually gummatous or papillomatous, and more common than early syphilis, though even at that, decidedly rare. Hematuria and a slow course mark all the reported cases, together with a rapid

response to treatment and a resistance to other measures. No undoubted case was observed to Stokes's knowledge in the Mayo Clinic during the years 1916 to 1944. Finsterer's review (1930) of 158 cases in the literature since 1900 plus 2 of his own ends with the statement that not one measures up to the standard set by Young, that spirochetes must be demonstrated in the lesion. Neurogenous (atonic trabeculated) bladder of tabes has been elsewhere described (Chapter XX).

Syphilis of the prostate is also rare but well authenticated. The total of reported cases approximates 25 Warthin described the microscopical pathology and demonstrated the presence of spirochetes in a case of early syphilis, and Starry has outlined the gross changes occurring with late syphilis. Lobe states that the condition shows no distinctive features on palpation, and may resemble any type of prostatitis, prostatic tuberculosis, or malignancy the diagnosis resting entirely on collateral evidence and the therapeutic test.

LATE SYPHILIS OF THE CERVIX, UTERUS, TUBES, AND OVARIES

Gellhorn and Ehrenfest have published the most critical study of syphilis of the female internal genitalia. Parker review of early syphilis of the female genitalia is quoted in the chapter on early syphilis (Chapter XI) With the exception of chancre of the cervix, the syphilids of the structures mentioned are among the comparative rarities of medical and surgical practice. The pelvic satellite adenopathy of the cervical chancre can be recognized by palpation according to De Gregorio and De Biasio (1939) Late syphilids of the cervix are usually gummas, with necrosis and ulceration. The process may extend into the cervix or involve the vagina. The ulcers are firm, often elevated, may bleed or present profuse discharge and are painless. They may appear at some distance from the external os. Their outline is sharp, their surface covered with lardlike deposit, easily removed, leaving a characteristic luster The surrounding mucosa shows very little inflammatory reaction. The use of caustics on a simple erosion may produce a deceptive fatty sheen.

Actual knowledge of syphilitic lesions of the uterine body is extremely meager A few instances of gummas of the uterine wall have been recorded, and gummatous changes may occur in the endometrium, with excessive rarity The weight of evidence favors the belief that the uterus, like the prostate, is the most immune of all body structures, to *Spirochaeta pallida*. Gellhorn has described what he feels is a case of malignant uterine syphilis, with necropsy

Syphilis of the fallopian tubes may exist, but there is no clinical evidence of the fact, according to Gellhorn and Ehrenfest Syphilis of the ovaries is an as yet indefinitely defined possibility Hasen states that he has seen an undoubted case, but apparently no one has as yet succeeded in demonstrating the presence of *Spirochaeta pallida* in the adult ovary Gumma of the pelvic cellular tissue, mistaken for malignancy is also reported.

Uterine hemorrhage is an undoubted clinical associate of syphilitic infection in women. Gellhorn and Ehrenfest observed it in 40 per cent of 147 women with syphilis of the internal genitalia. Its cause is as yet unestablished and cannot be uncritically accepted as due to a syphilitic process in either the uterus or the ovary The mere cessation of hemorrhage following treatment for syphilis does not demonstrate the syphilitic origin of the process. Favel regards hemorrhage as the chief symptom of uterine syphilis. The one case on which Stokes has notes was that of a woman of thirty-four with a definitely enlarged and boggy nonpregnant and nonfibroid uterus who suffered from severe metrorrhagia with moderate secondary anemia and a positive blood Wassermann reaction. There was no history suggestive of gonococcus infection or abortion, and the response to treatment for syphilis was prompt, the hemorrhage ceasing and the patient improving rapidly in general condition. Such case history does not, as Gellhorn remarks, prove the metrorrhagia t have been of syphilitic origin.

Amenorrhea is occasionally observed as an incident of the onset of syphilis in the secondary period and in association with profound cachexia in the later aspects of the disease. It presents no distinctive characteristics. One or two menstrual periods may be missed during intensive treatment for syphilis without ill effects.

LATE SYPHILIS OF THE FEMALE BREAST

Early syphilis of the breast includes chancre and the rare form of acute syphilitic mastitis seen in the secondary period. Stokes has had a case under observation which, in addition to a mild mastitis during the secondary period, developed swelling and tenderness of the breasts without marked inflammatory signs, as a form of relapse on two different occasions, during rest periods in treatment, with immediate response to resumption of treatment. Late syphilis of the breast includes chiefly gumma, a very rare complication, usually mistaken at the outset for carcinoma and the even rarer condition of diffuse tertiary mastitis which may occur in prenatal

syphilis. Adair has recently summarized the literature of 40 cases and reports one case as appearing among 1674 carcinomas. The gumma is hard, painless, circumscribed, and presents cutaneous involvement as in carcinoma. *It differs from carcinoma in the bizarre involvement of the lymph nodes (gummatous lymphadenitis)*; in the rarity of "orange peel" pitting of the skin, in the more rapid growth of the gumma, the usual immunity of the nipple unless the lesion is very near the early fluctuation and breakdown of gumma, and the positive serologic reaction and confirmatory evidence of syphilis. In practice, *differential diagnosis from malignancy will be aided by tissue findings.* The most recent reviews are those of Ross (1938) and Braunstein and Woolsey (1940)

SYPHILIS OF THE TESTIS AND EPIDIDYMIS

The testis, in contrast to the foregoing rare conditions, is involved in syphilis with frequency that approaches that of the bones and the skin. Slight degrees of syphilitic orchitis seldom come to clinical recognition, however, except in the course of series of routine complete examinations. Palpation of the testis is too frequently overlooked, and there are no symptoms to attract the patient attention. Diffuse interstitial sclerosis and gumma are the two recognized manifestations. Marked degrees of the former give rise to the so-called "billiard-ball" testis, a slowly developing



Fig. 908.—Typical gumma of the left testis, of the type often spoken of as "fungus testis. Gumma of the testis before ulcerative breakdown occurs is most often confused with sarcoma and teratoma, and after breakdown with tuberculosis. The relative painlessness of the syphilitic testicle is not an infallible symptomatic guide. A blood serologic reaction should be taken on every tumor or enlargement of the testicle, and therapeutic test yields, as rule, very rapid results.

enlargement without marked symptoms other than dragging or aching sensation due to increased weight. The testis becomes insensitive to pressure and there may be an accompanying hydrocele. Involvement of both testes may occur though the process frequently remains unilateral. In this form of the disease the epididymis usually escapes. The tunica vaginalis may become adherent to the testis. The process must be differentiated from tuberculosis, which very rarely affects the testis except secondarily to the epididymis, and then follows course of breakdown and ulceration more suggestive of gumma. Sarcoma is favorite diagnosis in billiard-ball orchitis of syphilitic origin, and is relinquished sometimes with considerable reluctance by the surgeon in the presence of positive blood serologic reaction. The response to arsphenamine treatment is rapid enough to justify an intensive therapeutic test in such cases, softening and shrinkage following quickly on the administration of arsphenamine. Following the involution of the process varying degrees of shrinkage and atrophy may remain. The acute orchitides of mumps, gonorrhea, and septic infection are not likely *to be confused with it, although Hanon states that there is an acute syphilitic* orchitis which may be confused with gonorrheal epididymo-orchitis.

Gummatous orchitis is less common than the billiard-ball type, but may develop in association with it. The initial lesion is nodule which increases in size, becomes adherent to the tunica nd the scrotum, and softens and breaks down. Nodules may be palpated at other points. The differential diagnosis from tuberculosis is often not even considered. In no case should lesion of the



Fig. 869.—A moderate grade of syphilitic elephantiasis of the scrotum, in this case definitely associated with suppurating gumma of the inguinal lymph nodes. The condition responded rapidly to treatment. Late syphilitic elephantiasic changes in the labia and the scrotum, often with ulcerative lesions, are rare, though more frequently seen in the colored than the white race.



Fig. 870.—Gumma of the epididymis. This is a comparatively rare lesion, though nodular infiltrates of small size would be more frequently detected if search were made for them. The blood Wassermann reaction was positive.

testis or even hydrocele be treated without blood Wassermann test, and in any doubtful case, regardless of the blood Wassermann findings, therapeutic test is wise precaution.

Lymphedema of the scrotum may be secondary to syphilitic epididymo-orchitis with involvement of the coats of the testis. Pseudo-elephantiasis resulting from obstruction of gummatous lymph nodes is shown in Fig 869.

Epididymitis of syphilitic origin (Fig. 870), according to Michelson and Herman and Klauder is lesion whose rarity is more apparent than real. A very rare form, associated with secondary manifestations and following an acut course, is described. McLachlan (1926) demonstrated *Spirochaeta pallida* in the puncture fluid of 2 of his 3 cases with early syphilis. As rule the condition is chronic, coming on later in the disease and associated with sclerosis and permanent changes. The epididymis is easily outlined and not adherent, and is occasionally somewhat nodular There may be moderate hydrocele. The elimination of tuberculosis may be very difficult and should always include nonspecific type of therapeutic test even if evidence of syphilis be present.

Gummatous epididymo-orchitis usually begins in the testis as single or several grouped nodules, and results in the fusion of the two structures into an adherent mass which readily includes the overlying skin and breaks down to form crateriform ulcer Hernia of th testis may occur

In all lesions which have undergone softening and discharge, examination may disclose tubercle bacilli if the process is solely or partially tuberculous.

SYPHILIS OF THE PANCREAS AND SUPRARENAL GLAND

The clinical differentiation of syphilitic from other forms of pancreatitis is impossible, and the symptoms are not infrequently entirely masked by those of the hepatosplenic complex. An interstitial and gummatous type of pancreatitis are described, the latter being said t times to produce small cysts (Wile).

Warthin and Wilson in 1916 discussed the coincidence of latent syphilis in diabetes on the basis of the autopsy experience of the Pathologic Laboratory of the University of Michigan, giving in detail the histologic changes observed in the pancreas of patients with latent syphilis. Six of 41 cases showed marked changes in the pancreas and 2 of these were in diabetics. They suggested that latent syphilis may be chief factor in the production of form of pancreatitis most frequently associated with diabetes, but that diabetes is not always coincident with severe degrees of pancreatitis. I subsequent study Warthin placed the pancreas ahead of the central nervous system, liver and spleen in order of frequency of involvement in his autopsy material. His citations of the literature from the clinical side call attention to the general opinion that syphilitic glycosuria or diabetes is comparative rarity

Stokes has notes of only 2 cases in which the connection of the diabetes and the syphilis was established to the extent of an indubitably positive therapeutic test. Moore rates the condition as uncommon, but not rare. Both his patients were males in middle life with strongly positive blood Wassermann reactions and adequate histories, but no constitutional symptoms of the disease other than glycosuria. One of them was markedly overweight. The glycosuria disappeared in both cases under treatment for syphilis without dietary measures.

Syphilis of the suprarenal is well authenticated, but rare. Fite in careful study of syphilis of the adrenal based on autopsies of 250 syphilitic infants states that spirochetes could always be demonstrated in the adrenal if they were found elsewhere. In his cases 40 showed some abnormality of the gland, the most frequent lesions being the perinephritis syphilitica described by Simmonds. It may occur in association (see review by Wile) with secondary syphilis or as late manifestation. The symptoms are those of Addison disease, with or without the pigmentary features. I the case under J.H.S. observation (reported by Rowntree) the pigmentary picture was not typical; for long time there was doubt as to the actual involvement of the suprarenal glands, although the patient response to epinephrine settled the question antemortem He died suddenly and at necropsy was found to have suffered destruction of the larger part of the cortex and medulla of both suprarenal glands. Warthin in 2 cases found *Spirochaeta pallida* in the gland cortex.

LATE SYPHILIS OF THE THYROID

Mention has been made of acute hyperthyroidism in the course of early syphilis, of iodide hyperthyroidism due to the action of the drug on adenomas of the gland, of the improvement of symptoms of neurosyphilis under treatment for coincident hypothyroidism, and of symptoms of hyperthyroidism under treatment for syphilis. Gummatous thyroiditis is comparative rarity of which Stokes has seen 2 cases, one of which had been operated upon. Sensar (1918) and Netherton (1933) review the subject in the American literature. The detection of the condition must depend upon collateral signs of syphilis such as can be obtained by the use of routine blood

serologic test. Late syphilitic sclerosis has been described by Simmonds. Suspicion of syphilis or carcinoma should be aroused by the hardness or woody infiltration of the gland. Adherence to or ulceration into the surrounding skin occurs in a number of cases, but was absent in Stokes cases. The process, according to the literature, may involve any portion or all of the gland, and rarely gives rise to symptoms other than those of pressure upon the trachea, which may be serious, and of myxedema, which only occasionally occurs. Symptoms of hyperthyroidism are very rare. The response to treatment is excellent in reasonably early cases, and both those which Stokes observed sustained no serious consequences. The differentiation from malignancy cannot be made on clinical grounds alone.

Syphilis of the Salivary Glands.—Moore and Kemp state that involvement of the salivary glands occurred in 0.07 per cent of syphilitics seen at Johns Hopkins Hospital. Chargin and Rosenthal have recently summarized the literature on syphilitic parotitis, adding 31 cases to the 37 gathered by Gerber previous to 1914. It is apparent that many cases have been mistakenly regarded as Mikulicz syndrome, in which involvement of the lacrimal glands also takes place.

Involvement may occur early or late in syphilis, the early cases being bilateral and running an acute course, the late cases commonly being unilateral and running the slow course characteristic of gumma. Chargin and Rosenthal state that suppuration occasionally occurs in association with early syphilis, and concomitant involvement of the testes has been reported by Mohr. The response to treatment is usually good.

Mikulicz Syndrome.—*The chief symptom of this variable syndrome is a chronic symmetrical painless enlargement of the salivary or lacrimal glands. The etiology is probably a chronic infection, tuberculosis and syphilis having been demonstrated in some cases, with the etiologic agent unknown in the majority (Bunting).* Clinically early lacrimation occurs, with bilateral painless swelling of the lacrimal glands. Ptosis or exophthalmos is usually noted and there may ensue bilateral enlargement of the salivary glands, the parotids being most commonly involved. In a considerable proportion of cases general glandular enlargement develops, and definite leukemic blood picture has been reported. Rowe emphasizes the frequent enlargement of the liver and spleen. Howard states that, in the absence of glandular involvement, the course is benign. Syphilis is responsible for from 10 to 20 per cent of cases, the diagnosis resting entirely on collateral evidence and therapeutic response.

Syphilis of the Pituitary Body.—The literature comprises 30-odd cases, including the reports of Fink (1933), Kennedy and Fisher (1934), Williams (1940). The symptomatology is that of brain gumma plus pituitary disease, and symptoms of the latter may be lacking. Acromegaly does not occur (Fink), the symptoms being those of hypopituitarism. Involvement of adjacent structures may give rise to thalamic symptoms, etc.

Simmonds' Disease.—The syndrome of pituitary insufficiency first described by Simmonds may be syphilitic in origin. The cardinal symptoms of this bizarre disorder are emaciation, falling of the teeth and hair, thickening and loss of luster of the skin, listlessness and pathologic sleep. Affected patients have the appearance and actions of premature senility and Calder has remarked on the similarity to hibernation. In 1700 autopsies in which Simmonds examined the hypophysis there were found 17 cases of metastatic carcinoma, 9 with evidence of syphilitic changes, 9 of tuberculosis, and 20 cases in which the pathology was due to emboli. In the records of 70 cases abstracted from the literature by Calder 7 patients had syphilis of various types. One case showed improvement under antiluetic treatment, in one case the pituitary atrophy was believed due to syphilis and in two cases gumma was reported on pathologic examination. Mention has been made in Chapter XX of the syndrome of diabetes insipidus in association with neurosyphilis and changes in the hypophysis.

Relief of headache and visual disturbances in acromegaly following antisyphilitic treatment has been reported by Schlesinger and by Mingazzini but other symptoms have remained unchanged. Schlesinger also cites several cases of dystrophia adiposogenitalis of hypophyseal origin in association with prenatal syphilis.

Syphilitic Elephantiasis.—Fifteen cases of syphilitic elephantiasis are found in the literature, the process being limited to the genitalia or lower extremities. Fournier described the condition in his text. McDonagh recognized the possibility of confusion with Sabouraud's elephantiasis nostras in sporadic cases, and studied his case carefully for the presence of streptococci, with negative results. This patient recovered rapidly under mercurial therapy. Marshall and also Ingram have reported good response to specific treatment. Ingram's is the only case due to prenatal syphilis. Special care will be necessary after World War II to exclude filarial elephantiasis

CHAPTER XXIII

SYPHILIS IN PUBLIC HEALTH AND MILITARY MEDICINE

A Critical Field.—Under the explosive force of war a whole series of discoveries and critical evaluations of old principles and methods is taking place. It is easy to be optimistic as one observes the spread of serologic testing as a case-uncovering method the shortening of the time of treatment under intensive methods the reduction of risks of serious reaction by newly devised antiarsenical drugs impending improvements in prophylactics and the fall in venereal disease incidence rates both in the American civil population since 1936 and in those under military and quasi-military control. It is equally easy to be pessimistic as one views the enormous extent of the problem the recent rapid rise in incidence in special situations and in nations whose records have shown previous favorable progress the slowness of educational processes; the inertia, not alone in the public at large, but in those by whom the work must be done the unrealistic impracticalities of some of the most important control devices such as prophylaxis the tremendous disseminative influences of war via both the armed forces and the population shift of total mobilization, the perverse genius of alcohol and commercialized sexuality in keeping wide open and even enlarging the channels of dissemination, and the now critical problem of an expanding promiscuity

The Magnitude of the Problem.—The Surgeon General of the United States Public Health Service, Dr Thomas Parran has evidenced his intention of giving to the problem of syphilis during the next decade, or longer a very substantial share of the energies devoted to public health in this country From a recent forceful summary by Parran and Vonderlehr (Plain Words about Venereal Disease, Reynal and Hitchcock, 1941) we quote the most recent and authoritative statements covering the situation in this country

> The estimated prevalence of syphilis in the United States is three million two hundred thousand. The three and fifth persons with syphilis are divided, one for one, between white and colored races. The per cent of syphilis in the nation population is 2.4 to 1.3 for white; 11.9 for colored. One in every 44 persons in the United States has syphilis now The ratio is one in every 77 white, and one in every 8 colored persons. Syphilis is nine times more frequent in the colored than in the white race. It is slightly more frequent in white males than white females in colored females than colored males.

The statistical experience accumulated in thus defining the problem has led to some recent reinterpretations which are described by Vonderlehr and Usilton (1943) as follows, and summarized in Fig 871 quoted from Table V of their article.

> "The new calculated rates of prevalence are higher than the Selectee prevalence rates, the differential increasing with the higher age groups. For instance, among white males, age 21 to 25, the Selectee rate per thousand tested is 10 the calculated rate 14. In the 26 to 30 age group, the Selectee rate is 21 (20.9), the calculated rate 33 (32.6), and in the 31 to 35 age group, the Selectee rate is 36 (37.7), and the calculated rate 53 Again, the Negro rates follow the same general pattern except for the youngest group here the Selectee rate is higher than the calculated rate."

One must bear in mind throughout these discussions that rates are given in terms of number of cases per thousand population, that the incidence or attack rate is the rate of appearance of

new infections, that the prevalence rate represents all forms of syphilis present in the population under consideration at a given time including those uncovered by serologic testing. In interpreting the important Selectee statistics for this country it must be recalled that prevalence among Selectees is based on a count of individuals with positive blood tests, and excludes all those who had at one time acquired syphilis, but as the result of treatment or spontaneous cure, had negative blood tests at the time of examination.

Methods Employed in the American Survey Program.—On the basis of one-day cross-sections (reports from physicians in selected areas of the number of patients under treatment on a given day) and other statistical determinations, it is now definitely known that the minimum number of persons in the United States constantly in need of medical care because of syphilis is 683,000 or 4 per 1,000 population. Annually in the United States a half million cases of early syphilis seek authorized medical care. There is a large though undetermined number of individuals acquiring the infection who neglect treatment until some late manifestation forces them to have attention. As Vonderlehr points out, the disease is never thought of as epidemic in the United States, yet annually there are twice as many new cases of syphilis as scarlet fever, thirteen times as many as diphtheria, twenty-eight times as many as typhoid fever and one and one-half times as many as tuberculosis. The attack rate for syphilis based on a New York State survey is two and a half times as great in cities over ten thousand as in cities under ten thousand, being 414 per 100,000 in the larger cities. The urban attack rate was 40 per cent higher than that for upstate

Fig. 871

THE PREVALENCE RATE OF SYPHILIS AMONG WHITE AND COLORED SELECTEES; AND THE CUMULATED NUMBER OF PERSONS ACQUIRING SYPHILIS BY END OF GIVEN AGE PERIOD FOR WHITE AND COLORED MALES BASED UPON 1936 TO 1937 AND 1940 TO 1941 ATTACK RATES

Prevalence Rate per 1,000 Selectees Examined			Cumulated Number Acquiring Syphilis by End of Given Age Period				
				Using 1936 to 1937 Attack Rates		Using 1940 to 1941 Attack Rates	
Age Group	White	Colored	Given Age	White	Colored	White	Colored
21–25	10.1	191.2	24	19.9	220.8	12.2	136.4
26–30	20.9	293.7	29	40.8	318.6	21.9	243.6
31–35	37.7	357.2	34	58.4	375.2	29.3	301.6

From Vonderlehr and Usilton, The Extent of Syphilis at the Beginning of World War II. Am. J. Syph. Gonor. & Ven. Dis., 27:686, 1943.

New York. Incomplete reports substantiate the statement that the incidence of the disease is higher in the south (see Fig. 872) owing to the presence of a large infected Negro population. Analyses of the age, sex, and marital status bring out conspicuously the youthfulness of those infected. It is estimated that one fifth acquired the disease before twenty and even that on a national basis 11,000 yearly acquire it between the ages of eleven and fifteen.

The trend of the disease in this country has been investigated as a significant guide to what will be required in its control. From 1919 to 1930 there has, of course, been a gradual increase in the rate of reported cases for the country as a whole. Special surveys have been made to avoid the obvious error of statistics based on mere increase in reported cases. From such consider cessions in special communities aggregating eight and a half million in population, it is apparent that the prevalence rate of syphilis increased between 1927 and 1933, 6.4 per cent; between 1930 and 1934 in Massachusetts it increased 1.5 per cent. The rate for the female increased twelve times that for the male. The morbidity surveys of upstate New York have shown an increase in the prevalence rate for all stages of syphilis of 24 per cent.

In contrast to this increase in reported syphilis of all stages, surveys of special localities for early syphilis have shown such figures as a decrease of 15 per cent between 1927 and 1933 in seventeen selected communities, a decrease of 21 per cent between 1927 and 1933 in Massachusetts; and of 45 per cent in upstate New York during the same period. This decline in early syphilis, it will be seen, is accepted throughout the world as one of the most notable and hopeful

criteria of public health control for the infection. Reported late syphilis increased in the respective groups above mentioned 11 per cent, 19 per cent and 60 per cent. Syphilis in pregnant women, on the other hand, offers a hopeful contrast, with striking declines in certain areas, such as the state of Massachusetts, in which Hinton' examination of the serologic reactions of nearly 8,000 pregnant women between 1918 and 1919 and 17,000 pregnant women between 1930 and 1934, indicated a reduction of 70 per cent in positives and 76 per cent in doubtful serologic reactions, in spite of the employment of much more sensitive tests for a nine-month period in 1934.

Cardiovascular syphilis, so far as available figures indicate, is showing a downward trend in spite of the upward trend of heart disease at adult ages in the general population. In 1914 at the Massachusetts General Hospital, 18 per cent of a group of cardiac cases were due primarily to syphilis, while in 1928 the proportion due primarily or secondarily to syphilis was 5 per cent. The reduction of 20 per cent occurred in aneurysms in the same hospital, and aortic insufficiency and aneurysm have dropped 40 per cent in the United States Army in the ten years ending 1934.

In the field of neurosyphilis, first admission rates for paresis in 500 institutions in the United States show no change from 1922 to 1933, while first admissions for other causes than paresis

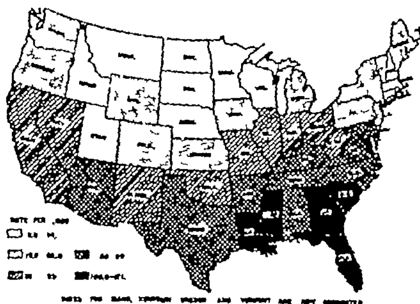


Fig. 372.—Two million selectees blood tested for syphilis. Rates per 1,000 tested for age, race and residence within each state. Reports received November 1940 through August, 1941 (Federal Security Agency United States Public Health Service).

have increased 17 per cent. In Massachusetts a slow decline in the rate for males has been apparent since 1920. Mortality data for paresis in the registration area of 1900 indicated a decline from 1916 to 1933. In New York and Massachusetts there has been a rapid decline from 1924 to 1927 but since 1928 the rate has remained stationary at 3.5 per 100,000 population. The death rate for tabes dorsalis declined from 3 in 1918 to 0.9 in 1933.

It is apparent then, that syphilis is a major if not the major national health problem. Vonderlehr and Usilton have summarized the pre-war status of the United States as of 1941 as follows

It may be reported that in the five-year period from 1936 to 1941, the chance of acquiring syphilis has registered a significant drop. It may be stated further that a new base has been established for measuring the effectiveness of syphilis control activities on the basis of prevalence, and that future measurements against the new base may be related to the pre-war chance calculations.

The precise extent of the gains made up to the onset of the war is summarized in Fig 871 The distribution of syphilis in the United States is graphically portrayed in Fig 872 and regionally summarized in Figure 873.

Smillie has published an interesting commentary on the significance of the foregoing types of figures syphilis as race problem. He contends that in the United States, it is neither an urban disease nor a disease of large cities and seaports; that industrial areas do not suffer to an unusual degree and that the extraordinarily high prevalence of syphilis in the Negro is the basic public health fact which permeates overwhelmingly all other data. The geographical distribution of the disease bears a direct relation to the distribution of the Negro population of the nation, and in those states having the highest syphilis rates in Negroes, there is concomitantly a higher-than-average syphilis rate in white men. The data indicate in his opinion also that syphilis may be brought under some degree of control in the Negro as well as in the white as in Massachusetts and Rhode Island for example. There has been tendency he contends, in official health circles

Fig 873.

PREVALENCE OF SYPHILIS IN SELECTEES AND GENERAL POPULATION*

Region	Selectees Rate Per 100†	General Population Est. Rate Per 100‡	General Population Est. No. Cases‡
United States	4 5	2 4	3,177,[illegible]
16 Southern States and D C	10 3	4 6	1,901,[illegible]
South Atlantic	11 2	5 5	834,[illegible]
East South Central	10 3	4 2	434,[illegible]
West South Central	9 2	3 8	497,[illegible]
32 Northern States	2 1	1 4	1,2[illegible]
New England	1 1	0 6	53,471
Middle Atlantic	2 2	1 4	376,[illegible]
East North Central	2 3	1 6	415,[illegible]
West North Central	1 7	1 2	[illegible]
Mountain	2 8	2 0	81,[illegible]
Pacific	2 7	1 8	171,[illegible]

* From Vonderlehr Bulletin of Genitoinfectious Diseases, Massachusetts Dept. of Public Health, January 1942

† Males, aged 21 35

‡ Males and females, all ages.

to gloss over or t ignore the high prevalence of syphilis in the Negro, and the sooner this truth is recognized, nd ppropriat steps are taken t deal with the situation, the better it will be for the Negro race and for the public health of the nation as whole.

Possible Sources of Error —The rapidly developing knowledge of the fallibilities of serologic testing should not be exaggerated as a possible source of statistical error but will undoubtedly require careful analysis. Certainly in figures which admit to consideration patients under treatment for syphilis in the practices of private physicians, there will be as there now very probably is in the armed forces, a significant group placed on treatment for biologic false positive blood tests. There is also some reason to suspect, though its qualifying influence may not be great that there may prove to be a special racial trend toward biologic false positiveness in the Negro that may influence statistics, as biologic false positives undoubtedly influence though slightly the general statistics, based on mass serologic testing It is hardly to be ex

pected however that these considerations will invalidate or reverse the important general principles above set forth.

Experience of Other Nations.—Declines in the incidence of syphilis have been experienced abroad especially in the Scandinavian countries in which the statistical evidence is most direct and Great Britain in which it is, in the main, indirect. It is wise to point out that declines in the incidence of syphilis demonstrable by figures are not necessarily due to public health practice. The existence of waves in the epidemiologic curve of syphilis has been pointed out by von Düring and Gumpert and suggested by Källmark's mathematical analysis. There has been no general demonstrable decline of syphilis throughout the world despite the modern advances in treatment control and educational effort. Substandard treatment has been responsible for bringing to a standstill programs and prospects such as the Belgian, which seemed at the outset certain of success (Schwers) The adverse influence of travel, of fluid population, of heterogeneity in language and race, and of the limited value over a period of years, of publicizing educational methods, has probably left its mark on the progress reports of many countries. The effectiveness of the Scandinavian program for the control of syphilis is conventionally estimated statistically from the incidence rates in three representative cities in 1919 as compared with 1934. In the city of Copenhagen the rate fell from 597 to 28 per 100 000 (divide by 100 for comparison with American rates) in Stockholm the rate declined from 450 to 7 per 100 000 in Oslo, the decline was from 350 to 30 per 100 000

In a country like Great Britain whose practice has had rather more in common with American procedure than the Scandinavian, there are unfortunately no absolutely definitive statistics. The number of cases dealt with for the first time in treatment centers throughout England and Wales has, according to the annual report of the Chief Medical Officer of the Ministry of Health for 1935 been reduced from the peak of 1920 (42,805 cases) to 19,535 in 1935 This represents a 55 per cent reduction and indicates that the volume of syphilis has declined within fifteen years, since the peak, to 45 per cent of the original figure. Known cases of syphilis with infections of less than a year's duration have been reduced from an incidence rate of 2.28 per 10 000 population to 1.47 per 10 000 population in the five-year period 1931–1935 This is a reduction of 35 per cent. The death-rate from infantile congenital syphilis has been reduced by 86 per cent from the peak year of 1917 to the low of 1935

The Effects of War.—The tradition, well established by experience, is that war increases the prevalence of venereal diseases in both civil and military populations. For the armed forces, as presently indicated, the rise in incidence during past wars is easily demonstrated. There are, however no figures at present available, or likely to become available until after the present war for the influence of this conflict on venereal disease incidence in American civil life. One must turn, therefore, to foreign experience, not too satisfactorily delineated, for some indication of what we may expect. Colonel Harrison states that the actual increase in venereal disease in the British civilian population in World War I is unknown, but some idea of it may be gathered from the number of service men who were infected (416 498 British and Dominion soldiers) and from the fact that in 1917 the mortality in infants certified as due to syphilis was nearly twice that in 1913 (ten times that in 1939) and that in 1938 the crude mortality rate of women from aneurysm of

large blood vessels, a disease most commonly due to syphilis contracted many years previously was two and a half times the mortality from the same cause in 1921 The Chief Medical Officer of Scotland reports for the period of World War II that the number of newly infected patients attending civilian treatment centers was 6 433 in 1939 6,851 in 1940 and 10,179 in 1941 The Glasgow figures for new infections were: 1939—300 1940—590 1941—909 The Edinburgh figures were 1939—199 1940—230 1941—444 This amounts practically to a doubling of the incidence of syphilis in Scotland in three years under war conditions. Colonel Harrison reports that in comparison with the rates for 1939 the incidence of early syphilis increased 31 per cent in 1940, 70 per cent in 1941 and 120 per cent in 1942.

While these are the facts, their explanation is as yet not completely determined. The state of affairs they depict should not be too readily ascribed to the presence of a nonresident or foreign army population from nations with differing or lower standards of sexual conduct and so forth. The problem

Fig 674.

OSLER'S REVISION OF BRITISH MORTALITY STATISTICS IN TERMS OF SYPHILIS

	Total	Estimated persons with syphilis
Diseases of the nervous system	58,000	
General paralysis	2,963	2,500
Locomotor ataxia	733	733
Other diseases of the cord	2,616	1,500
Cerebral hemorrhage (apoplexy)	23,485	5,000
Softening of the brain	1 478	[illegible]
Paralysis without specified cause	2,965	[illegible]
Other diseases of nervous system	14,000	2,000
Diseases of the vascular system		
Aneurysm and aortitis	1,141	1,000
Organic disease of heart	46,000	5,000
Diseases of arteries	10,000	2,000
Total	173,383	19 496

Syphilis is responsible for 11 9 per cent. of deaths from nervous and vascular diseases

reflects as much as anything the necessity for use of every resource at whatever cost for the control of the epidemic sweep of venereal disease in time of war The prevalence of syphilis in the armed forces of the United States will be summarized later but at this point it is well to emphasize the general principle that the civilian population is, broadly speaking the source of venereal disease and not the reverse. This makes the figures for the incidence of venereal disease in civilian populations particularly critical and makes the difficulty of securing them under war-time conditions of shortened budgets and reduced personnel especially regrettable

Morbidity and Mortality of Syphilis.—The importance of syphilis as a cause of death cannot be precisely defined. It has disappeared in a forest of symptoms ranging from apoplexy and chronic myocarditis, cirrhosis of the liver Banti's disease adrenal cachexia, uremia in tabes dorsalis, and some of the obscure pictures of syphilitic encephalitis In spite of this beclouding of the situation, attempts at reinterpretation of various categories of the listed

causes of death have apparently indicated that syphilis outranks both pneumonia and tuberculosis as a fatal disease Osler's revision of British mortality statistics in terms of syphilis still stands as probably the most suggestive estimate available (Fig 874)

While Osler placed syphilis, as result of this study first among the causes of death, Downing' reinterpretation of the Massachusetts statistics places it fourth (one death in eighteen) preceded by tuberculosis, pneumonia and cancer Salmon in New York State found that general paresis alone among the innumerable modes of death from syphilis to date stood eighth in the mortality tables, and that it is responsible for one out of every nine deaths between the ages of forty and sixty years.

An interesting study of principal reason why mortality statistics in syphilis are of little value was that carried out by the Westchester County Health Department in New York State (Nicol and Bellows 1934), in which it was apparent that hen physicians were assured that their death certificates were confidentially filed, the reporting of syphilis as cause of death was practically doubled over the original figures. A tabulation of deaths exclusive of stillbirths, and death rates in the United States in 1930, 1934, and 1935, quoted by Nelson and Crain (1938) from the United States Public Health Service Weekly Reports for April, 1930 shows that the reported death rate for syphilis, tabes dorsalis, and general paralysis of the insane was 13 4 per hundred thousand population in 1935 The rates for 1934 and 1930 were 14.0 and 14.1 respectively According to the Westchester County experience, these rates should be doubled to correct for incorrect returns.

The death curves for acquired syphilis have been computed for United States experience by Usilton and Miner (1937) Life expectancy of males with acquired syphilis is shortened from that in the general population from ages thirty to sixty by 17 per cent in the white males and 30 per cent in the Negro males.

Parran (*Shadow on the Land, 1937*) *estimated that syphilis caused 18 per cent of all deaths* from heart disease, but pointed out that this figure required revision because of the inclusion of Negroes, who have an exceptionally high death rate from cardiovascular syphilis. Syphilis accounts for 10 to 18 per cent of the total deaths from cardiovascular disease, and actuaries estimate that the verage patient with cardiovascular syphilis has twenty-two years less to live if untreated, than his normal contemporary Since persons with cardiovascular syphilis die sooner after the disease becomes apparent than other heart disease patients, the proportion of deaths is higher than that of other cases. Of 160,000 Americans with cardiovascular syphilis, 40,000 die each year death rate of one in four Of 2,340,000 Americans with other types of heart disease, 273,300 die each year death rate of one in eight and half In estimating the incidence of cardiovascular syphilis in latent and late syphilis Parran gives figure of 18 per cent based on 17 600 patients.

THE SOCIAL AND ECONOMIC COSTS OF SYPHILIS

The cost accounting of syphilis has the same elements of sketchiness as the estimates of its mortality The chief value of figures is impressionistic and bolsters campaigns for funds more than it illuminates the practice of public health *syphilology* On the other hand, the critical meaning of cost to public health versus private practice care of the disease the extension of laboratory testing facilities under modern standardization procedures which shows some of the characteristics of the production methods in industry the place of free drugs and hospitalization in a program and the costs of clinic, contact tracing and case holding, are real contributions to the brass tacks of syphilis control. In Fig 875 we have summarized the more important categories of figures in a résumé by Beerman (1940) which provides as much tangible information as is generally available.

Clinic versus Private Care and the Costs of Foreshortened Methods.—Attention should also be drawn in this tabular summary (Fig. 875) t comparisons of the cost of private and of clinic care,

as

and to the one available statement regarding the cost of foreshortened intensive treatment in early syphilis (five-day drip) These baseline figures constantly appear in the recent literature in arguments to extend the fields and methods concerned because of their cost availability For example, in the most recent acquisition t the treatment of syphilis, figures are already beginning to appear as to the cost of an eight-day cure in terms of gradually improving methods of manufacture of the agent employed. The ribald suggestion has already been made: "Make the cost of acquiring greater than the cost of cure.

Federal and State Appropriations for Venereal Disease Control.—The figures for the national program are the basis of extremely important estimates for appropriations such as the LaFollette-Bulwinkle National Venereal Disease Control Act passed by Congress in May 1938 This Act

Fig. 875

SOME "COSTS" OF SYPHILIS

1 Cost of national "curative" program, 518,000 cases per year		$14,000,000 to 25,000,000
2. Cost of Hospitalization		
Hospitalization and direct relief (Moore estimate, national scale)	per year	$53,000,000 to 80,000,000
New York City (Goldberg)	per year	$1,000,000
3. Cost in Labor Lost (man hours) in industry (estimate) at $5.00 per day standard treatment, national scale		$83,000,000
4 Costs of Laboratory Tests (actual)		
2400 tests per year	per test	$1.03
6000 tests per year	per test	.56
50,000 tests per year	per test	.29
200,000 tests per year	per test	.18
5 Costs of "Free" Drugs (Health Department purchases)		
Baltimore	per year	$7,000
Buffalo	per year	2,000
Philadelphia	per year	11 000
6. Direct Costs to Cities (special studies)		
Baltimore	per year	$170,000
Buffalo	per year	103,000
7 Per Patient Costs		
a. "Cure private care, standard systems		$300 to 370
b. Cure fresh infections, national program scale (Moore estimate)		25 to 40
"Cure, present clinic practice, at $1.00 per treatment patient visit		75 to 100
		75 to 85
d. "Cure, five-day drip		11.21 to 11.50
Contact tracing and case-holding per year		$15,500,000
8 Cost of Neurosyphilis, New York State, 1931	per year	$10,000,000
9 Cost of Blindness from syphilis, national scale.		
10 Cost of Cardiovascular Syphilis (hospitalized)		
Baltimore		$11,000
Buffalo		8,000
11 For City Budgets, see Fig. 880.		—

Summarized from Deerman, H. Am. J Med. Sci., 190 596, April, 1940. —

authorized $3,000,000 for Federal assistance t the states during the first year $5,000,000 during the second and $7,000,000 during the third year Parran relates that in Jul 1911, a budget bureau cut of more than 50 per cent of the authorized amount was immediately countered by action from the House of Representatives, practically restoring the entire appropriation. In the heyday of expenditure during World War I, have an interesting baseline for program estimates in that the National Government provided $2,700,000 for a single year's program. When recall that the Chamberlain-Kahn Act t its expiration left the program precisely the level, we can realize the really tremendous growth of national purse consciousness, each ascending year after year provisions, of the importance of venereal disease control in several years

An essential part of America's policy is that the states shall be dr to participate at

national program by dollar matching system. For example, in 1938 the State of Pennsylvania appropriated for venereal disease control the sum of $184,000 which was "matched" by $197,000 of Federal funds; Massachusetts in 1937 appropriated $300,000 which was then "matched" by $67,000 of Federal funds. According to Vonderlehr (1942) there was an increase of 24 per cent over 1940 in the budgets of Federal ($6,400,000), State ($3,000,000) and local funds ($3,800,000) for 1941, the third year of activity under the Venereal Disease Control Act of 1938. Of necessity Federal grants in aid must go in increasing proportion to parts of the country where the need is greatest and the per capita capacity to pay is least.

THE GENERAL VENEREAL DISEASE (SYPHILIS) CONTROL PROGRAM

Extent of the Field.—Syphilis should be considered with other venereal diseases because the program of its control extends far beyond merely medical measures. In fact, a major deficiency in syphilis control has been the tendency to focus so closely upon the medical and particularly the treatment aspects of the disease that the full front of the attack was lost in consideration of a single sector. In order to visualize the sectors of the front and the agencies over which syphilis control is distributed, Fig. 876 has been prepared as a teaching program guide against which it is possible to measure the coverage of any individual set-up as well as the direction and development of project plans.

The Grand Strategy.—While the grand strategy of control of a venereal disease may have a central headquarters from which directives issue regarding fronts and agencies, the essence of the control of venereal disease is a local and not a central problem. In the last war all those concerned with venereal disease control, and indeed the public at large, were vigorously impressed at the start by a tremendously positive expression of its intention by the Federal authorities, with the necessary implementing laws to back it. The local disease control agency had its arm strengthened often well in advance of the apparent need, by such implements as Sections 12 and 13 of the Selective Service Act of May 24, 1917, which provided a quick action mechanism for the clean-up of local bad spots. Impressed with the value of such central policy, one is apt to lose his awareness of the fact that local conscience and local practice provide the really lasting foundations of successful venereal disease control. No central policy directive such as this can entirely take the place of the way the home folks feel about it. Even under organizational discipline in the armed forces, the official in charge at a given point distant from the policy forming authority exerts a large personal influence on conditions for which he is responsible, orders from headquarters notwithstanding. Above everything else, a venereal disease control program leaning heavily on vice control and law enforcement in civilian life (Items 6–12 inclusive of the agency groups in Fig. 876) is almost completely at the mercy of local backing. It does not operate by general principles; it sidesteps central direction and is therefore a method with distinctly limited possibilities for the wholesale control of the spread of disease. Such considerations as these make the endless repetition of individual set-ups at individual points where venereal disease is a critical issue an unavoidable necessity. The detail of some of these local groupings is subsequently considered in connection with the armed forces.

Program Types.—Notwithstanding what has been said with reference to the essentially local character of successful venereal disease control solutions, there are program types on a national scale whose basic principles have wide application. A parallel column of the Scandinavian and British types appears in Fig. 877.

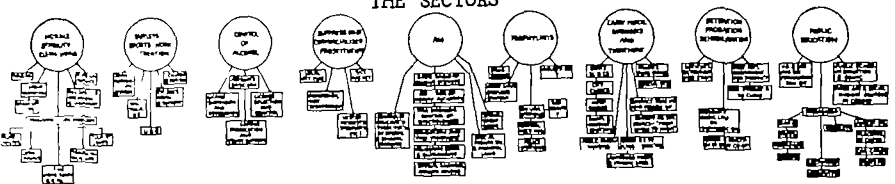


Fig. 876.—A blueprint of venereal disease control.

The United States is at the moment drawing its practice largely from the Scandinavian example. The Scandinavian plan of venereal disease control is probably the oldest in the world the most thoroughly systematized and rests on the most permanent foundation of national character national homogeneity and national intelligence of any body of health legislation in the world (Clarke, 1936) It is essentially an enforcement plan which takes education for granted. It is perhaps to be expected that from Scandinavian sources, the legislatively minded will draw inspiration which unfortunately is not always as effective in a new milieu as its proponents expect it is not received by nor has it the educational and constructive effect on a different type of mind that those who frame it, desire. In contrast with the Scandinavian technic stand the experiences of countries like Great Britain and the Netherlands, in which law and enforcement play a negligible part. While successive surveys of the situation in these two countries before the war tended to disclose results approximating those of the Scandinavian countries, the acid test is now in process of appli-

Fig. 877

PROGRAM TYPES IN VENEREAL DISEASE CONTROL

Scandinavian (Regulation) Type	British (Voluntaristic) Type
1 Complete basic legal structure and respect for law	1 Extreme or ultra-democratic voluntaryism (no compulsion)
2. Reporting and central registration.	2. No reporting or identification.
3. Complete compulsory authority vested in health authority and sanitary police	3. No contact-tracing or treatment attendance follow-up.
4. Treatment obligatory	4. Treatment not obligatory but made attractive as inducement (especial emphasis on convenience)
5. Treatment free for all.	5. Treatment free for all.
6. Advertising (full public)	6. Advertising (conservative).
7 Public education (conservative)	7 Public education (conservative)
8. Punishment for wilful transmission (seldom invoked)	8. No punishment.

THE AMERICAN TYPE IS DISCUSSED IN THE TEXT

cation and insofar as it is possible to appraise results, the shortcomings of a purely voluntaristic plan under certain war emergency conditions are for the moment more apparent.

The American Program.—The stage has been set for the American program by first, the development of standards of medical practice by the work of the Cooperative Clinical Group and the United States Public Health Service in association with the League of Nations Investigation repeatedly referred to in this work second the building up of prestige for the movement by the outspoken expressions and policy of Surgeon General Parran of the United States Public Health Service. Challenged at the start by the refusal of one of the national broadcasting companies to permit him to discuss the subject of syphilis over the air his persistent efforts in the matter have enlisted the interest and cooperation of even the most lethargic members of the medical profession, the press and the public. In fact, so active has the press become that "scoops" are occasionally in print almost before the originators of methods and ideas have clarified their own thinking. The third potent influence is, of

course the provision of the sinews of war in the form of funds under the Social Security Act and subsequent Congressional and State appropriations.

The general outline of the American program can be obtained from the report of the Advisory Committee to the Surgeon General, published by the United States Public Health Service in January 1936. This program provides that the state, municipality or health district which plans to open a campaign against venereal diseases should integrate this work with the Communicable Disease Division of its Health Department, but give it separate direction and a high individual autonomy implied by a full-time venereal disease control officer. A local advisory committee to the health department, coordinating the interests of the venereal disease division, the medical and allied professions and all voluntary agencies, is to be established in each of these jurisdictions. An adequately organized program and proportionate assistance determined by the state venereal disease morbidity rate, are provided for. Adequate treatment facilities in urban communities are to provide (1) for the diagnosis and emergency treatment of any patient who applies, or (2) of any patient who is referred by a private physician either for continued treatment or for consultative advice and opinion, (3) finally, for any patient who is unable to afford private medical care. The establishment of clinic facilities is to be made a matter of conference among various instrumentalities concerned, including medical school, local hospital, research and philanthropic societies with the local organized medical profession and the state and national public health service. Polyclinics are preferred to isolated clinics and the support of subsidized hospitals and health centers is made contingent on their cooperation in the state program. The admission of patients to beds when required for the treatment of syphilis and gonorrhea is made a condition of continued support. Provision is made for the development of a record system for transient and transferred patients. In communities with inadequate treatment facilities, surveys are provided for, followed by a conference of all concerned and a full discussion of the question of enlisting the cooperation of local practitioners, organized branch clinics, new clinics, health education and so forth. The need for abolition of quack remedies and drugstore prescribing is emphasized. In rural communities, emphasis is laid on subventionary assistance of properly qualified local physicians, the services of specially trained county health officers, special provision for transportation of patients to centers and the development of large special treatment centers in areas such as the deep South where many Negro patients are concentrated. Travelling health units are also suggested. It is stated that the free distribution of antisyphilitic drugs by the state to all sources of treatment is rational and proper, and it is advised that two arsenicals and one bismuth preparation be the minimum made available in such a program. The development of a venereal disease diagnostic and treatment center of high rank in each state is strongly urged to serve as a consultation agency for patients, the profession and the clinics throughout the state.

For the first time in its history the venereal disease control movement gives full cognizance to the great importance of epidemiologic work in the control of the disease. Coincidentally follow-up (case holding), long a species of stepchild in the majority of syphilis clinics, has received new and more serious recognition. Both these fields are now conceded to require careful special training for those who devote themselves to them.

In the matter of laboratory facilities the Advisory Committee has unhesitatingly urged the standardization by the state of all serodiagnostic procedures with the maintenance of a careful check even to the point of licensing of private laboratories performing this work. The effects of such recommendations and the results secured are more fully considered in the chapter on serologic tests. In the matter of morbidity and mortality reports, the American program provides for the reporting of all cases by a numerical system including a place of residence if not the name of the patient. Laboratory reports are not to be accepted as case reports. An exceedingly important feature of the modern venereal disease program is the informative and educational program for physicians. There can be no escaping the conviction after a study of this problem that the most serious difficulty confronted by a venereal disease program in a country such as the United States, where a large proportion of patients with syphilis receive treatment at the hands of private physicians, is that of raising the physician's standard of knowledge and technic to that of the modern clinic or above it.

Public Health Law — The issue of compulsion versus voluntarism which appears above in Fig 8— strikes through every question involving the control of venereal disease by laws. In the United States two sharply distinguished and opposed schools of thought exist, the majority we believe favoring legislative sanctions as essential parts of a venereal disease control program affect

they are to be used with discretion and with an appreciation of their educational as well as their compulsory worth. Broadly speaking however we subscribe to the belief that the voluntary approach should be permitted to do its utmost before any attempt is made to use the teeth which the program may provide. It has repeatedly been the testimony of experts who have had at their disposal every resource of police and other forms of compulsion, that the cooperation of the infected individual is vital to a successful epidemiologic approach. Unless the "from whom to whom" principle can be freely applied and elicit a generous and wholehearted response from the victims of the disease in whatever social category they may be found a program will inevitably suffer by the flight of the victims from the agencies which wish to help them.

Public Health Law in Venereal Disease Control.—The field of legal control is marked by two distinguishing facts the evidence of the American's liking for a law and the disposition to write a law on an isolated item or situation whenever such may be brought to a legislator's individual attention. The combination has produced a curious patchwork tissue of state enactments and fragments of enactments, many of them conflicting and anachronistic and many of them without adequate basis in either medical or public health knowledge. Moreover since syphilis has been the proverbial shocker of the legislative mind and the center of social hygiene activity most of the laws concern syphilis and as such fall far short of the requirements for general venereal disease control. The American Social Hygiene Association has been particularly influential in the effort to clear the confusion, systematize the requirements and formulate a standard form of law for the control of venereal diseases which can serve as a reference guide to individual groups making plans. This law is based on certain basic principles summarizable as follows with respect to syphilis. (From Stokes and Ingraham, J.A.M.A. 112 1113 1939.)

Laws regulating the control of syphilis should take account of the enormous variability in individual cases and the positive necessity for expert medical interpretation wherever serious question arises. Laws governing syphilis will tend to be too specific if drawn in too great detail. Insofar as they preserve the right of the state to allow its public health officers to decide by individual local or official regulation in a flexible manner the processes of enforcement and judgment, subject to cooperative interpretation by the court, they are likely to be good. Insofar as the enactments tend to define in days and weeks and to specify in degrees of positiveness and negativeness of the specific tests, they will tend to run into difficulties both in the infliction of injustice on individuals and in unenforceability in the light of expert testimony in the courts. A proposed public health law should be drawn in sufficiently general terms to permit an adequate exercise of individual expert medical judgment and to provide for public health expediency in the individual case without invading the province of morals. In thus allowing adequate exercise of expert medical judgment it is a further though unfortunate necessity that some provision must be made for the prevention of evasion through connivance between patient and physician. This contingency is well met in the New Jersey law for example, which grants to the health officer of the jurisdiction the power of review over medical decisions in individual cases, and even power to appoint his own medical examiner to check the original findings. No single test or single procedure uncontrolled or unchecked should be allowed to make a diagnosis of syphilis. This applies even to the darkfield identification of *Spirochaeta pallida*, a procedure in which even the reasonably experienced may make serious mistakes and over which some form of control and expertness in judgment should be exercised. The limitations of serologic testing have been adequately discussed and emphasis has been repeatedly placed on the difficulties encountered by the venereal disease control officer in his need for definitions of infectiousness and noninfectiousness and his attempts to obtain it (see p. 167). Special legislation for the control of venereal disease should then obviously not be written to depend purely and simply on laboratory tests.

The operability and effect of venereal disease control legislation is materially influenced by a number of considerations, some of which become evident only on an actual attempt at enforcement of previously framed legislation or ordinance. An excellent example and one of the oldest

course, the provision of the sinews of war in the form of funds under the Social Security Act and subsequent Congressional and State appropriations.

The general outline of th American program can be obtained from the report of the Advisory Committee to the Surgeon General, published by the United States Public Health Service in January 1936 This program provides that the state, municipality or health district which plans to open a campaign against venereal diseases should integrate this work with the Communicable Disease Division of its Health Department, but give it separate direction and high individual utonomy implied by full-time venereal disease control officer A local advisory committee to the health department, coordinating the interests of the venereal disease division, the medical and allied professions and all voluntary agencies, is to be established in each of these jurisdictions. An adequately organized program nd proportionate assistance, determined by the stat venereal disease morbidity rate, are provided for Adequate treatment facilities in urban communities are to provide (1) for the diagnosis and emergency treatment of ny patient he applies, or (2) of any patient who is referred by a privat physician either for continued treatment or for consultative advice and opinion; (3) finally for any patient who is unable to afford private medical care. Th establishment of clinic facilities is t be made matter of conference among various instrumentalities concerned, including medical school, local hospital, research and philanthropic societies with the local organized medical profession nd the state and national public health service. Polyclinics are preferred to isolated clinics and the support of subsidized hospitals and health centers is made contingent on their cooperation in the state program. The admission of patients to beds when required for the treatment of syphilis and gonorrhea is made condition of continued support. Provision is made for the development of a record system for transient and transferred patients In communities with inadequate treatment facilities, surveys are provided for followed by a conference of all concerned and full discussion of the question of enlisting the cooperation of local practitioners, organized branch clinics, new clinics, health education and so forth. The need for abolition of quack remedies and drugstore prescribing is emphasized. In rural communities, emphasis is laid on subventionary assistance of properly qualified local physicians, the services of specially trained county health officers, special provision for transportation of patients t centers and the development of large special treatment centers in areas such as the deep South where many Negro patients are concentrated. Travelling health units are also suggested. It is tated that the free distribution of antisyphilitic drugs by the state to all sources of treatment is rational and proper and it is dvised that two arsenicals and one bismuth preparation be the minimum made available in such program. The development of venereal disease diagnostic and treatment center of high rank in each state is strongly urged to serve as consultation agency for patients, the profession and the clinics throughout the state.

For the first time in its history the venereal disease control movement gives full cognizance to th great importance of epidemiologic work in the control of the disease. Coincidentally, follow-up (case holding) long a species of stepchild in the majority of syphilis clinics, has received new and more serious recognition. Both these fields are now conceded to require careful special training for those who devot themselves t them.

I the matter of laboratory facilities the Advisory Committee has unhesitatingly urged the standardization by the stat of all serodiagnostic procedures with the maintenance of careful check even to the point of licensing of private laboratories performing this ork. The effects of such recommendations and the results secured are more fully considered in the chapter on serologic tests. In the matter of morbidity and mortality reports, the American program provides for the reporting of all cases by numerical system including place of residence if not the name of the patient. Laboratory reports are not to be accepted as case reports. An exceedingly important feature of the modern enereal disease program is the informative and educational program for physicians. There ca be no escaping the conviction after study of this problem that the most serious difficulty confronted by venereal disease program in country such as the United States, where large proportion of patients with syphilis receive treatment at the hands of private physicians, is that of raising the physician standard of knowledge and technic to that of the modern clinic or above it

Public Health Law.—The issue of compulsion versus voluntarism which appears above in Fig 87" strikes through every question involving the control of venereal disease by laws In the United States two sharply distinguished and opposed schools of thought exist, the majority we believe favoring legalistic sanctions as essential parts of a venereal disease control program al…

is a species of understanding between courts and health officers as to the best method for meeting the hygienic purposes of the law with due regard for the rights and liberties of the individual.

The questionable value of routine food handlers examinations in controlling the dissemination of syphilis and other communicable diseases under the usual circumstances is well portrayed by Best (1937), who lists the reasons for abandoning this practice in New York City in 1931 after eleven years active trial, as follows (1) the average physician examination cannot be considered reliable. (2) The cost of adequate examination with attendant laboratory procedure is prohibitive and not commensurate with the public health benefits obtained. (3) Even though complete examinations are made, there is no assurance that the food handler will remain free of communicable disease during the tenure of certification. (4) The value of this procedure in preventing the spread of communicable disease such as syphilis is much over-rated.

What has been said with regard to food handlers' examinations applies with equal force to the again much discussed examination of prostitutes, for example, which recognizes them as an occupational class and presumes to indicate that their infectiousness is determinable at any and all times, or at stated times by an examination procedure of routine type. Conductors and dining car waiters, who for years were the only individuals in railroad personnel subjected to any type of examination specifically for syphilis, are probably as far removed from the danger field so far as the public is concerned, as any single group. Gross and improper extensions of the spread of law when it is freed from the individual case are well illustrated by a laboratory worker for example, with congenital syphilis, who because he worked for a milk processing organization was discharged from employment though his contacts were with chemical reagents and had nothing to do with food.

Under the legislation of the past decade, enforcement when projected into the courts has usually been at the expense of what might be called the relatively down-and-out types—persons of no reputation and questionable or "floating" standing in the community against whom it was relatively easy to secure authority from a court for summary action such as examination, detention, and quarantine. It is not to be concluded that the application of summary legislative procedure will be so readily accepted by persons of character standing and resource, as the spread of these laws increases. The question as to whether any person may be obligated under any conception of civil liberties, to undergo testing or examination for the mere existence of disease (and particularly disease implying rightly or wrongly moral turpitude) has had some consideration in the courts, and there have been decisions which have denied to a plaintiff the right to oblige a person under trial to undergo either physical examination or blood test to determine his status with respect to syphilis. It will, therefore, be doubly necessary in order to protect legislation against adverse judicial decisions, to place the responsibility for the interpretation of the blood test not with the law itself but with the physician or properly authorized public health representative.

It has been recognized for some time by claim and damage authorities that when a case involving syphilis as a contributory factor in compensation is brought before a jury it is fundamentally bad policy and likely to lead to adverse decision to force the evidence of syphilis in the injured person before the jury for adjudication. The jury apparently tends to take the view that in attempting to attach syphilis to the issue the defending attorney is endeavoring to besmirch the reputation of the pleader and to deprive him of just compensation on a character irrelevancy.

The question of secrecy and confidence always important in medical matters, has a double importance in all that concerns venereal disease. The mere statement of the law that the record of the test will be filed in confidence with the *state health authorities can be received as only* qualified assurance. Leaks unquestionably can occur and cannot be traced to their sources. The distrust of physicians for this confidential aspect of records is evidenced by their short comings in reporting. Privileged communication and record is an issue in the legal aspects of syphilis. Under Acts of the Pennsylvania Assembly in 1907 for example, hospitals, which are common sources of Fonting information on syphilis, have no right to give data from their records disclosing communications with physicians attending a patient in a professional capacity or information which would tend to blacken the character of the patient without the patient's consent. The sole exceptions are civil cases brought by the patient for damages on account of personal injuries. The constant violation of this law exemplified by correspondence between social service agencies for example, in which positive serologic reports are bandied about without regard to the responsibilities involved, or the protection of the persons concerned, is characteristic. Confidential privilege may be waived by the patient, and such waiver might conceivably be made a stereotyped part of a contract relationship as it now so generally is in life insurance policies.

The Individual Physician.—The individual physician who is medicolegally wise will not disclose information regarding a patient with syphilis to any source except under instruction of legal counsel, unless he is protected by a full release of such information over the signature of the patient. It is even well to be sure that the signature of the patient is genuine

THE PUBLIC HEALTH MECHANISM

General Principles of Control of an Infectious Disease.—The control of syphilis stems from fundamental public health principles which, if kept in mind make clear the purposes of the pyramid of organization which rests upon them and explains some of the avoidable and unavoidable conflicts between public health and private practice which too often stand in the way of disease control. An infectious disease is dealt with by (1) immunization, (2) isolation, (3) sterilization of the infected individual and (4) education of the public with respect to prevention Immunization against syphilis does not exist. Isolation and quarantine in the days of prolonged infectiousness and slow treatment at least, were a practical impossibility used only from time to time as an enforcement demonstration or for flash publicity in special situations. With the development of rapid methods of treatment, quarantine and isolation judiciously applied may grow in importance but since they violate the fundamental principle of voluntaristic control they are, wherever possible second rather than first choices Under war pressure such devices as rapid treatment centers will have their day and their need but their value as permanent constructive solutions of the transmission problem should be closely scrutinized Education of the public, as will presently be seen from a fuller discussion, has between inertia and impracticality an extremely difficult road to travel. There remains therefore, for the control of syphilis, the fundamental public health principle of sterilization of the infected individual. To devise the means for such sterilization, freeing the individual of the infective organisms as completely and rapidly as possible with the smallest possible risk to his life and health is the present *summum bonum* of public health practice in this field. The tremendous advances that are being made in this direction with the shortening of treatment requirements and the use of increasingly effective reactionless spirillicides may make unnecessary a considerable part of the present elaborate structure of public health control.

Organization, Costs and Budgets.—In order to draw adequate control plans, prepare the treatment set up and justify to the public and his constituency the organization and expense involved the health officer must have constantly before his mind the necessity for determination of the prevalence and distribution of the disease with which he is dealing As reporting is popularized and case uncovering more and more fully developed, the disproportion that exists between the cases that become matter of record and pursue uneventfully their treatment course towards infection control and cure and the vast unmeasured body of unidentified disease and suspected or recognized disease which evades or fails to obtain adequate treatment becomes increasingly apparent

As specific example of the importance of thus mapping the ratio between practice and ideals, the experience of Philadelphia is clear but probably not exceptional. Under Ingraham's administration of venereal disease control, the treatment prevalence of syphilis as it might be called (syphilitic persons under treatment) obtained by review of each of the established treatment agencies and 89 per cent of the practicing physicians experience in the community showed

Fig. 578.—Organizational Chart of City Department of Public Health Venereal Disease Control Program. The arrows indicate the directions of supervision or service from the central administrative office. Numerals within the squares show the number of locations or the strength of the staff in each position as the case may be. This is based upon the 1943–44 budget of the City of Philadelphia Venereal Disease Control Division with staff of 113 full time and part time individuals and an annual expenditure of approximately ten cents per capita as outlined in the text on p. 1206.

that in 1940–1941, 4.5 syphilitic persons per thousand population were under treatment. As a result of intensive work by the Division of Venereal Disease Control this had been increased to 7 per thousand by 1943. Contrast this, however with the actual prevalence of syphilis as shown by Selective Service examinations, surveys of occupational groups, particularly in war industries, and the result of premarital and prenatal legislation. The actual prevalence rate of syphilis in this area lies between 28 and 35 per thousand. Thus, despite great efforts and now approximately adequate financial provision for venereal disease control, only about one-fifth of the patients who should be receiving treatment are under medical care. In all probability part of the discrepancy is due to the fact that case-uncovering is a slow process that must be carried along over a period of years to be completely effective.

The type of organization deemed most effective for venereal disease (syphilis) control has already been outlined in general principle, on p. 1196. To give these general principles point, Fig. 878 has been drawn up by Ingraham to present a type of organization applicable to cities (Philadelphia) and in principle also to larger units. This set-up emphasizes what we conceive to be the modern requirements for case-finding in the form of contact-tracing mechanism and the liaison with various possible sources (e.g., the municipal courts) of infectious material. It also shows the

Fig. 879.

ANALYSIS PHILADELPHIA VENEREAL DISEASE CONTROL PROGRAM BUDGET 1943–44

			Annual Expenditure
1.	Central Administrative Office		$14,110 00
2.	Epidemiology and Attendance Follow-up		66,310 00
	a. Central Registry	$7,310 00	
	b. Central Epidemiologic Unit	33,500 00	
	Clinic & Field Service	14,000 00	
	d. Medical Social Work Consultation and Investigation	7,600 00	
	Consultation Court Cases	3,800 00	
3.	Treatment of Patients		91,731 00
	Medical Service	34,391 00	
	b. Nursing Service	18,400 00	
	Clerical and Janitorial Service	21,140 00	
	d. Drugs and Medical Supplies	17,800 00	
4.	Education Staff and Materials		5,700 00
5.	Miscellaneous expenditures (fixed equipment; replacements; repairs; rent; communications; stenographic, clerical and janitorial supplies)		11,400 00
	Total		$187,701 00

relatively large amount of effort necessary to classify and identify (under suitable protection) the infected individual and to see to it that he pursues treatment to a satisfactory outcome. In other words, a public health organizational set-up which consists simply of clinics for the treatment of individuals is inadequate by modern standards. A very large part of the budget will have to be devoted to reducing the discrepancy between patients under treatment and patients who ought to be under treatment, the quick identification of the infected individual on the street, and the permanent placement of the infected individual in the public health reconstructive program until he has ceased to be a danger either to the community or to himself. It will be recalled that the fundamental principle of free treatment will necessitate a considerable mechanism for the distribution of drugs both to clinics and to private physicians. It will be necessary moreover to expend time, personnel and effort in behalf of those functions of the private physician in public health relationship which he performs with difficulty or which he cannot perform at all (contact-tracing and case-holding).

The budget of an effective venereal disease control unit on a reasonably large scale as above outlined is illustrated in Fig. 879 and shows the tax-payer exactly where his appropriation goes. The largest single item is, of course, treatment, but the epidemiology and attendance follow-up is a close second, and uses 35 per cent of the total available funds.

In order to provide for the control of a large-scale infectious disease situation such as that represented by syphilis, it is desirable as early as possible to give the public some idea of what an effective program should cost. The studies of the past several years, represented particularly by the larger cities, are given in Fig. 880 The per capita basis of cost is now commonly set for an effective program at 10 cents. Cities, such as Chicago, which are trying expensive and important experiments in treatment centralization, easily demonstrate the quick rise in cost which an energetic campaign, involving centralized agencies such as treatment centers, may entail. One of the beneficent effects of war has been the quick acceptance by appropriating agencies of responsibility for bringing their per capita allocations in this field up to the ten-cent standard.

Significance and Appraisal of Educational Effort.—The venereal disease control officer should never give a merely casual acceptance to alleged educational methods and material. In the end his whole program rests upon the case that he can make for the seriousness of his problem, and the prospects of solving it. Accordingly while he subscribes to and uses propaganda, he recognizes its shortcomings, and labors unceasingly to bring to the potential and the actual victim of the disease the knowledge of how to avoid and how to meet the situation.

The last war (World War I) gave the United States an unusual opportunity to test the effectiveness of public education on really massive scale, in the attempt to saturate two million soldiers with what the constituted authorities considered adequate information on venereal disease. Direct methods of ppraisal lacking, an indirect clue to the effect of all this effort consisted in raising of the proportion of patients between 1916 and 1930 who reported t clinic within the first ten days of their syphilitic infections from 2.4 to 4.3 per cent. For examinations within the first fifteen days, the proportion rose from 24 to 35 per cent in fifteen years. It would be unjust, of course, to suggest that this glacial type of advance represents the best that can be done by didactic speech-making, lecturing and the leaflet type of informative propaganda. An attempt to carry the question more directly int the field made by the United States Public Health Service and the American Social Hygiene Association jointly (Edwards and Kinsie, 1940) dealt with the ill-defined but critical question of drug-store prescribing and the common man warenses of what to do if and when he acquired the venereal diseases. This paper (Venereal Disease Information, Vol. 21, p. 1 January 1940) should be read in the original by all those obliged to expend effort on the educational sector of the venereal disease front. Using "plain clothes observers, this study disclosed in 23 cities, 62 per cent of 1,151 drug-stores visited as willing to diagnose and sell remedies for syphilis or gonorrhea; 31 per cent would not diagnose but did sell remedies, especially if asked for by name; only 7 per cent refused to diagnose or sell. In this study it ppeared that the man in the street when asked for advice as to where to go to get fixed up for venereal disease, responded t the extent of 65 4 per cent with advice to the inquirer to seek drug-store, drug-store remedy or self-treatment. In 1935 similar questions had elicited "bad advice in 57.3 per cent and "good advice in 40 per cent.

Not only is there, then, the ever-present stolidity and stodginess of the established, the inertia of the human mind, but conspicuous lack of adequate study of which methods teach what, and how they do it. It is essential before education can mean what it should in the venereal disease field that, among other things, we better understand the human mind, and the modes and motives by hich it resists and absorbs new material. Whether educational forces must be brought to bear purely as matter between individuals or in the mass, through the eye, or through word of mouth is all still unclear The bursts of educational fervor in the press; the introduction *of syphilis int the status of "a cozy household word" as deKruif has put it, are worth a kile, but* partake unfortunately of wave-like ephemeral quality—a flash impressionism and passing worth. It is essential, therefore, that in his public educational work, the health authority be not satisfied alone with posters, moving-pictures and speakers, but shall concern himself with the systematized steady pressure of effort in the home, for example, in the school, in general hygiene education, and so forth. He must be constantly alert to the fact that while good influences are surely expanding and permeating, pornography lubricity and all the forms of literary and cinematic frankness and over-stimulation are not giving ground. No field places greater pressure

Fig. 860.

VENEREAL DISEASE APPROPRIATIONS IN VARIOUS LARGE CITIES IN THE UNITED STATES

City	Population	Source of Funds				Venereal Disease Expenditure Per Capita Based on	
		Federal	State	Local	Total	Local Appropriation	Total Appropriation
Baltimore	834,144	—	—	$83,203	$83,203	$0 092	$0 098‡
Boston	770,816	$28,777	$72,183	16,900	117,860	0 022	0 153*
Chicago	3,400,000	401,000	16,000	258,000	805,000	0 079	0 250‡
Cincinnati	455 610	20 000	—	27 780	47 780	0 061	0 104
Detroit	1 730,000	50 000	—	90 000	140,000	0 051	0 08*
Los Angeles	1 661,000	46,170	12,810	94 780	148,780	0 057	0 087†
New Orleans	550,000	41,933	—	31,370	73,303	0 059	0 136†
New York City	7,927,000	317,300	—	411 600	728 100	0 059	0 108*
Philadelphia	1,937,349	116,100	—	81 661	197 761	0 042	0 101
Pittsburgh	671 659	84,314	—	37 013	121,301	0 055	0 18*
San Francisco	675,000	58,086	7,030	66,715	129,831	0 099	0 192*
St. Louis	814 717	900	55,590	47 916	104 106	0 058	0 127*

From 1945–46 Budgets † From 1946–47 Budgets ‡ From 1940–41 Budgets

upon the public health officer to concern himself with all the broadly human relations of his disease problem than does that of venereal disease control. Though the effectiveness of educational methods in venereal disease control is estimated with difficulty when the public at large is the subject, the increasing budget, the increasing proportion of voluntary cooperation in case-uncovering, mass and individual, the increasing proportion of patients under treatment, as compared with infected individuals identified, provide basic measuring material.

The Cooperation of the Physician.—In the equally important undertaking of educating the medical profession to cooperation, the circular letter the personal questionnaire the activity of the county and state medical society in the field as a result of the venereal disease control officer s efforts to contact the physicians of his jurisdiction, the non-responsiveness on the part of the private physician frequently lamented by the health officer may be a matter of technic.

The public health authority in Philadelphia found, for example, that the placing of request in the bulletin of the county society for the names of physicians willing to treat venereal disease brought only approximately forty responses. When an adequate explanatory letter with reasonably framed and brief questionnaire regarding the physician practice interest and actual venereal disease clientele was mailed to every physician in the city 2600 replies were received from the group of 3300 practicing physicians. Of these, 1600 stated that they treated venereal disease, and 1100 expressed willingness to have patients referred to them by the City Venereal Disease Control Division. Contrast this with the forty replies to the notice in the Weekly Roster It is increasingly apparent that campaigns that consume their own smoke are direct appeals to the key persons in groups in the public health situation involved, and have much better prospect of return on the educational effort than fire-works discharged over the heads of the public at large

Mechanisms—Reporting Case-Finding, Statistics.—Two methods of reporting are at present in use. The first is the individual physician s venereal disease report card to State or municipal public health headquarters, which is so often a mystery even to consultants in venereal disease that a typical example with its appropriate instructions is given in Fig. 881 This form of report card provides for the (optional) use of a number instead of a name and address, the name and address usually being supplied only in the case of delinquent and uncooperative persons. Clinic reporting in a large proportion of the clinics of the United States is at present conducted through a central tabulating system developed and described by Usilton of the United States Public Health Service to whose description reference should be had (Venereal Disease Information, 21 61 March 1940) The information collected on the forms is transferred to punch cards which make possible the precise evaluation of the clinic material, the contact-tracing and the follow-up efforts included. Adequate reports of clinic performance are returned to the source on a monthly basis. The tabulating centers are allocated on a state or regional basis.

Case-finding involves the individual personalized mechanism for finding the infected person described under "patient control," below and the employment of mass serologic testing which has become prominent in the past few years. The first requisite to a wide employment of mass serologic testing whether legally sanctioned or voluntary is a dependable laboratory system. The really colossal mass serologic survey of the Selective Service System would have been impossible without the years of spade-work in the development of adequate state and municipal laboratories whose test results could be trusted. An approval system for private laboratories must be developed parallel. The public health officer controlling syphilis must not let his enthusiasm for case-finding lead to undiscriminating use of mass testing methods.

The margin of error is sufficiently serious and the interpretative difficulties sufficiently great so that he must provide for adequate evaluating mechanisms both for the sake of the individual case discovered and for his statistical records as a whole. In setting up mass testing demonstrations, it is necessary to make it clear to cooperating physicians that serologic reports are not case reports and that individuals with positive serologic tests must be examined. It is, we believe, bad practice to set up any mass testing demonstration in which the tested individuals are supplied direct with the results of their blood tests.

VENEREAL DISEASE REPORT

Disease — Date————

Gonorrhea ☐ Syphilis—acquired ☐
congenital ☐

Other venereal disease ☐

Please name—

Is patient in communicable stage? Yes ☐ No ☐

Approximate date of

IDENTIFICATION OF ORIGINAL PATIENT

Age————

Is this new case? Yes ☐ No ☐

Is the patient now under treatment? Yes ☐ No ☐

Serial number of previous report if any————

Do you wish us to follow? Yes ☐ No ☐

IDENTIFICATION OF CONTACTS

Please supply information concerning source of infection or of individuals who may have been exposed to infectious venereal disease.

Address

Relation to patient if any

Address

Relation to patient if any

Address

DRUG REQUISITION FORM
FOR LOW FEE VENEREAL DISEASE PATIENTS

Dear Sir:

Please send me supply of the following drug(s) for the treatment of the patient

1. ☐ Whose new case report is attached
2. ☐ The serial number of whose previous report is

Please check or indicate quantity desired:

—	Neoarsphenamine	0.45 Gm. amp.
—	Neoarsphenamine	0.6 Gm. amp.
—	Mapharsen	0.04 Gm. amp.
—	Mapharsen	0.06 Gm. amp.
—	Sulpharsphenamine	0.1 Gm. amp.
—	Sulpharsphenamine	0.3 Gm. amp.
—	Sterile distilled water	10 c.c. amp.
—	Bismuth Subsalicylate in oil	30 c.c. vial
—	Bismuth sodium tartrate 1.5%	60 c.c. vial
—	Bismuth sodium tartrate 1.0%	60 c.c. vial
—	Sulfathiazol tablets	0.5 Gm.
—	Other (please name)————	
—	Patient Educational Material	
—	Venereal disease report forms	
—	Easy mailing envelopes	

M.D.

Fig. 881.—Venereal disease report card. This report card serves a fourfold purpose and may be used to (1) report venereal disease; (2) report a delinquent patient for Health Department action; (3) report an individual who has been exposed to a venereal disease; (4) request drugs for the treatment of low fee patients, literature for patient education, and additional report cards. All information is kept confidential by returning in the enclosed business reply envelopes, postage to be paid by the Health Department.

Self interpretation under such circumstances is only too common, and the name of the home or referring physician to whom to send the report should be supplied by the patient or the patient should be told to visit a physician (preferably name and address given) to receive the interpretation of his result. The mechanism for the interpretation of serologic tests has been sufficiently discussed in Chapter IV.

The statistics obtained by the foregoing types of effort are the beginning and not the end of the venereologist's troubles. Discarding summary judgment, such as "lies, damn lies and statistics," it may well be insisted that the

public health authority should scrutinize and rescrutinize and publicize only after such scrutiny the results of all forms of case-finding efforts.

An excellent illustration of a typical problem in statistical epidemiology is provided by the experience of Philadelphia, following the reports of syphilis incidence based on Selectee statistics. In the Journal of the American Medical Association, an authority made the statement, "Philadelphia, with a rate of 41 7 per thousand, has the highest rate among the cities of one million population or more. Ingraham as Venereal Disease Control Director for the City conducted with the cooperation of the Public Health Service, which was the source of the statistics an analytical study based upon race, age and sex distribution figures from these same Selectee statistics, a survey which brought out the following facts: the rate through August 1941 for 14 of the largest cities in the country shows that Philadelphia with a rate of 8.5 per thousand among its white Selectees and volunteers, has the lowest rate in the country of any city of comparable size except Milwaukee, and with a rate of 182.2 per thousand among its Negro Selectees, is eighth from the top: San Francisco, Chicago, St. Louis, Los Angeles, Washington, D C., Buffalo, and Baltimore all having higher rates. In other words, a critical analysis of "flash" epidemiologic statistics, indicated that Philadelphia, far from having the highest, may have one of the lowest syphilis rates of the larger cities in the country

Spot mapping is often the highly useful visual aid that follows statistical epidemiology This type of pin-placement on a map provides the graphic inspiration for campaigns as well as a vivid demonstration to legislative sources of funds.

Sterilization of the Infected Person.—This, the key to the disease control situation in syphilis, must not only be clear to the venereal disease control officer and all his personnel, but must be sold as a treatment concept to the medical profession and to the public. The principles involved have been fully discussed under the control of infectiousness and in connection with the various drugs used in treatment.

The seriousness of a mistake in national policy in selecting an inferior spirillicide as the sentimental or economic choice over an arsphenamine was illustrated by the experience of pre-war France in which Jeanselme for example, was able to present to the French Dermatological Society evidence indicating that the national preference for bismuth, as a French discovery over salvarsan, as a German discovery had led to a serious prolongation of the infectious period of the disease in the individual patient. The struggle of the health officer to pin the syphilologist down to a "treatment to noninfectiousness" standard as a matter of budgetary economy and simplification of follow-up has been mentioned. Curiously enough "20–20" (20 arsenical and 20 bismuth injections), never actually proposed for the purpose by the authorities credited with it, has increasingly established itself as a fairly dependable amount of treatment for the reduction of the aggregate infective material to noninfectiousness. In the establishment of a time-interval between lapse or failure to report and time of reporting an individual case to the health authority the efficacy of an arsenical must be borne in mind, and two weeks is the maximum period (1 per of two treatments) that it is safe to allow before reporting by name is insisted upon. Similarly it is necessary to bear in mind, and to bring home to the practicing physician, the existence of treatment-resistant syphilis which fails of sterilization by the arsenicals, or expresses itself in repeated infectious relapse, particularly after a small amount of irregularly administered therapy. The oncoming of intensive treatment for early syphilis, plus the pressure of war emergency plus the prospect in the offing, of an extremely effective spirillicide whose administration is a reactionless nondangerous procedure compressible into approximately a week, is likely to transform many of our conceptions of the public health technic of sterilization of the infected individual. The rapid treatment center as a method of removing and "cleaning up" the most tarnished element of the community may ultimately find itself extended in the larger municipalities, especially to mass hospitalization comparable to the Chicago fever treatment center fully described by Sandeson, Bauer, Kendell and collaborators (J.A.M.A. 123:816, Nov 27 1943). Insofar as this simplifies or reduces the cost of multiple state management of the problem of infectiousness, it may be rated as an advance.

Compulsory Treatment or Quarantine.—Florid methods of dealing with the venereal diseases are of course, to be deprecated but compulsion must at

times be exercised This the health officer has authority to do under the general health law of the state or municipality through the use of a court order or bench warrant, either by incarcerating the person in a contagious disease hospital or quarantining him in his home under placard. Relatively little use is made of the last method mentioned, but the authority to do so is one of the most important of the resources of the health officer in dealing with the venereal diseases.

An essential element of this authority repeatedly supported by the courts is the doctrine of "reasonable suspicion," which makes possible the tremendously strategic examination of the patient as part or sequel of his quarantine or isolation as reasonably suspected" source of infection. The prostitute falls under special criminal classification in both the public health and criminal law and, upon conviction as a prostitute, she can be subjected both to examination and detention without further action. As will presently appear the examination and detention-on-suspicion technic is falling afoul under war emergency pressure of the many problems connected with complaints against a source of infection. In this country so generous has been the law's interpretation of the authority of health officer that almost anything not too palpably outrageous can be expected to work in an emergency but this does not justify the undiscriminating use of authority to force examination and detention as primary resource in dealing with local critical dissemination problems. It is always wise after the emergency is over to back-track; examine the legal standing of the methods employed, and then, if it seems desirable, to introduce by way of ordinance and enactment such measures as may make extrajuridical forcing of the public health authority less necessary

Free Treatment Clinic versus Doctor, and the Indigency Line.—In his obligation to provide free treatment (and incidentally free diagnosis to those who need it) the health officer in this country must take cognizance of the fact that 55 per cent of the physicians engaged in private practice do not treat syphilis at all. Slightly more than 50 per cent of all patients known to have the disease are treated in clinics. In some areas (St. Louis, for example), 65 per cent of syphilitic individuals are cared for by 5 per cent of the physicians. It is clear that of necessity therefore the clinic must be an important and indeed a major instrument in the treatment mechanism. A practical demonstration of its importance is found in the figures given by Vonderlehr which show an increase in the number of State Health Department clinics in the United States from 1 122, in 1938, to 3,245 in 1941 to meet an increase in case load from 140 434 to 340 615 This increase in number and responsibility is taking place despite the easily recognizable and to some extent inevitable limitations of the clinic as a mechanism for handling venereal disease. Clinic practice in the United States was rated in 1930 as only 25 per cent efficient, and for the potential case load only 10 per cent.

MacNealy and Pearson (1937) presented a devastating indictment of the venereal disease clinic practice of this country pointing out the lack of basic understanding of the problem, the limited scope of service the desultory extraclinical investigation, the incomplete recording of significant information the failure to utilize appropriate diagnostic aids; and the failure to control irregularities in treatment as primary and almost omnipresent defects. The international investigation by the League of Nations Commission disclosed not only inadequacies in diagnosis and treatment among the selected clinics of the world but that clinic chiefs themselves were unaware of the procedure of their own clinics and lived in dream-state in which their conceptions of ideal practice and the methods of their clinics showed no conformity whatever Notwithstanding all these strictures, however clinic practice can be made to align itself to a presentable degree with high modern standards and in many cases does better but it even at worst, than the general practitioner of the same area does at best.

The basic requirements for a good clinic may be listed as follows (1) a properly chosen head or director ideally full time or at least half time whose

personal enthusiasm inspirational power and standing as an expert are paramount. (2) The remainder of the staff must be not only professionally adequate but of a human type that enlists the cooperation not to say the affection and trust of the patients. (3) The physical equipment of the clinic should provide for privacy and if at all possible, the separation of the sexes. (4) Privacy is particularly essential in the preliminary history-taking and subsequent contact-tracing and case-holding interviews, and in the physical examination of the patient which should take place in an individual room or cubicle (5) Darkfield apparatus, in the present organization of most public health clinics, is essential (6) Equipment for the giving of treatment, which is plentiful enough and maintained in sufficiently good condition so that no disgraceful short-cuts can be justified and discomfort to the patient, that ever-present cause of lapse, shall be minimized. (7) Since it is preferable that clinics be part of general medical and diagnostic centers rather than *ad hoc* beds for the care of the more serious aspects of syphilis, for the isolation of the infectious case and for the treatment of neurosyphilis can and should be available. This does not mean however that every individual clinic for the mass treatment of syphilis should have electrocardiographic and fluoroscopic equipment. (8) Day and night clinics are essential. (9) So far as possible, infants, children and adolescents and congenital syphilis and pregnant women are to be taken care of in special groups.

McKneely and Pearson (1937) list, as evidence that clinic has obtained reasonable degree of perfection when there exists clear comprehension on the part of the administrators of the problem in all its aspects; an inclusive service reaching all types of cases maternity cases in particular an effective plan for seeking sources of infection, contacts and delinquent patients, and for observing temporarily those discharged an accurate system of records giving personal history physical findings, serologic tests and treatment response of each applicant; an adequate diagnosis based on history physical examination and appropriate laboratory tests, and the use of an accepted scheme of treatment adapted to the needs of the individual.

The indigency line cuts directly across the clinic s organization and problems, and is the chief source of controversy between private and public health practice in this field at the present time. Unquestionably if the health officer will temper his zeal for ideal results by accepting and indeed seeking private medical cooperation, extraordinarily effective response may be forthcoming Suspicion and misunderstanding, on the other hand will lead to a stymie which is sometimes extremely serious, especially when a medical society with a well-organized legislative program and floor representation takes the field. The result of a personal approach to a large group of physicians in a city area has been presented on p 1205 Consistent assurance that the case-uncovering methods employed are not intended to recruit patients for state or city clinics, but that uncovered cases will be turned over to private physician cooperators who are genuine cooperators, very quickly opens the door to better understanding. In addition, an active effort to make available to the busy practitioner consultative service and instructional programs, usually meets with excellent response. The teaching methods employed should be preferably those of case-teaching, individual consultation, demonstration *before small groups in a suitably* equipped setting—rather than lectures, orations and formal scientific papers, though the latter if reinforced by visual and printed summaries and material, may be made effective. The popular radio broadcast, the use of lantern-slides and moving-pictures, are, in our

opinion, distinctly second in worth to methods based upon the actual demonstration of case or technic.

Consultation by correspondence has been presented t some extent on p 136 to indicate the type of question in which the practitioner is interested. Such consultative aid is unquestionably desirable, but may be limited by the malpractice laws and interpretations of the locale in which it is to be developed. A study of medical educational requirements for students suggests that fifty-six teaching hours, 250 pages of text, and demonstration of 80 to 100 actual patients in the third curricular year are reasonably effective. The minimum which the student needs for a public health program is the ability to collect and mail specimens, interpret reports, prepare and properly inject the best spirillicides and heavy metal preparations; ability to control and prevent reactions to master schedule for early and prenatal syphilis; t keep out of trouble in latent and lat syphilis, and cooperate willingly with the state and individual consultants in their special responsibilities and procedures.

Patient Control.—Some of the most important developments in the past decade of public health practice have been in this field, and the whole subject needs to be understood better by the private physician, in order that he may avail himself of state service, and thus contribute enormously to the control of the disease Case-finding has been discussed in its mass-testing aspects. Individual case-finding or contact tracing is an art rather than a science Effective case-finding like effective case-holding or follow-up, begins not as the patient leaves, but as he enters the physician s office or the clinic. Upon the impress made in the first interview and specifically the impress made by the physician quite as much as the specialized worker depends all the future success or failure of the effort to find out, from whom to whom" the infection has passed and to induce each and every source and carrier to begin treatment and pursue it to recovery

The original contact tracers were first, public health officers, such as Munson, ho deserves the credit for originating the present-day emphasis on the epidemiologic approach to the disease, and ho hunted it from point to point as the carrier moved, in what he called "mole-leather epidemiology His work and principles were taken up and expanded by social orkers such as Jal MacPhillips nd Louise B Ingraham. Their work made it clear that the contact tracer is not an occupationally classified individual ith diploma and certification, but an adept who combines number of qualities not necessarily confined to medical or nursing public health personnel. It has been one of the interesting observations of World War II that wide variety of people, provided they have human—one might almost say salesman or salesman-detective—approach, make excellent contact tracers The most strikingly original work done by physicians in the United States has been that of Smith nd Brumfield at the University of Virginia. Studies of the technic and problems of contact tracing and follow-up have indicated superiority of the voluntary approach over compulsion or enforcement tactics which ca be stated in percentages, as summarized by the Ingrahams. Their ork indicates that the employment of confidential persuasive approach to elicit voluntary response from the patient, in the hands of trained individual, is about half again as productive of usable epidemiologic information as is the untrained coercive approach. This applies also to persuasion of the contact to submit to medical examination. The natural" who does this work most successfully has the true sleuthing and portrait-classifying type of mind. Clues such as bent lamp-post at an assignation corner a cast in the eye tint of hair some quirk in the method by hich the prostitute contact "rolls" the victim, provide the basis for building up identities in remarkable fashion. When it is considered that the source of much contact tracing material is the befuddled if not intoxicated individual, the difficulties which the verage doctor may encounter in tracing the source can be imagined.

In order to make clearer the picture of the contact tracer as one of the most important instruments of present public health venereology Fig 83! has been prepared

Individual case-finding has revealed, as nothing else has ever done before, the trickle of venereal infection, syphilis specifically through all strata of the community and over the entire country-side. Particularly effective diagrams in the trousers and skirt pattern are reproduced in Figs. 883 and 884 The latter by E. Gurney Clark, illustrates the interweaving of husband, wife and children into the fabric of prostitute and prison over the country-side from state to state and town to town. It is clear despite the obvious duty of the physician to whom an infectious patient presents himself to find out "from

Fig. 882.

THE CONTACT TRACER (EPIDEMIOLOGIC WORKER)

1 The contact tracer is person, male or female, who has, or can develop, the knack of (a) getting venereally infected person confidence; (b) getting the names and whereabouts of the sexual contacts before and after development of disease; (c) persuading all persons exposed t come in for medical examination.
2. A contact tracer must be trusted and trustworthy in the estimation of wid range of people including ( ) the family (b) the young beginner (c) the frightened or the nonchalant, (d) the merely weak, (e) the amoral and asocial, (f) the vicious, (g) those ho have social and personal stake in concealment.
3. A contact tracer must be voluntarist—must think of force last, not first, as contrasted ith enforcement practice. In this lies the secret of his capacity and power
4. A contact tracer must know something of the diseases, the gonorrhea, "the ropes (local, political, legal, professional) and in war the military and naval channels and set-up.
5 A contact tracer must have catalogue mind and photographic memory comparable t that of the best enforcement and detective officer
6. A contact tracer must know his "territory" intimately if he is responsible for regional problem—the whereabouts of infected persons (treatment register), of local infection groups, of treatment facilities, etc.
7 A contact tracer must be incorruptible preserve the professional confidence, be entrustable with records.
8. A contact tracer must have the personality art and persistence to get his man (or woman) in whatever situation he (or she) may be found; on the street, in the taproom, in the brothel; in the parked car or over the kitchen stove, behind the counter or at the machine; in the dra ing room or the hot spot, in the hospital or clinic.
9 A contact tracer may be "natural, intuitively equal to all these roles, or trained specialist in one or more of them, as the visiting or public health nurse is in the family
10 The principles of effective contact-tracing can be taught but personality is the key

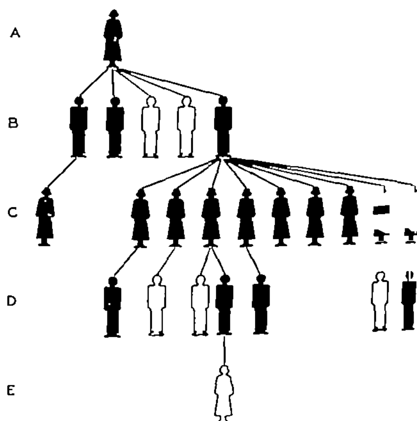
The qualities of training that make good contact tracer make good person to induce patients to continue treatment until cured. This is called case-holding" or "follow-up" and where the duties are combined one speaks of "contact-tracing and case-holding personnel.

whom to whom," that unless he is himself adept, he will need an interested specialized assistant to unravel even the more ordinary chains of distribution.

I "The Management of Syphilis in General Practice, the United States Public Health Service has outlined the commoner types of investigation of contacts, emphasizing the obligation t present fully to the infected individual the reasons hy it is necessary that he be requested to expose the details of his personal conduct, of his sexual experiences and partners. He must know that his contacts may not experience warning symptoms such as his which indicate the need for medical care an inadvertent tragedy may follow his failure to share his knowledge and his warning with them. Resentment against his supposed infector may be reduced to minimum by showing him that he voluntarily risked infection and that the individual from hom he has acquired his infection is likely as blameless as he is in illfully spreading the disease. I the case of marital partners, the question of infidelity presents complication of more serious nature, but tactfully handled it is by no means insurmountable. The promiscuous husband can often seek safety in

admitting premarital exposure; others must find their means of inducing husbands or wives to be examined through various ruses when overt confession seems impossible. The contact is best approached through the informed original patient, but when this means fails, other methods may be resorted to, and the health authorities called in. To provide the patient with even the phraseology with which to approach his contact, to meet the family complications where infidelity has occurred, through established round-about approaches to a problem seemingly in-

HOW SYPHILIS SPREADS



BLACK FIGURES PERSONS EXAMINED AND FOUND INFECTED
OUTLINE FIGURES CONTACTS EXAMINED BUT NOT FOUND INFECTED

Fig 883.—A physician in a middlewestern city asked the State Health Department to trace the source of infection in 5 cases of newly acquired infectious syphilis in his practice, all men (*B*). The infection of all 5 was traced back to 1 woman, *prostitute* (*A*). Then the inquiry turned to persons whom these men might have infected. It was discovered that 1 man had infected 1 girl, and another man 9 girls, of whom 8 were under 18 years of age (*C*). Of these, 4 girls in turn infected 4 other men (*D*). In all 21 persons were examined and 18 were found infected and placed under treatment. (Data furnished by the Minnesota Department of Health. Chart by the American Social Hygiene Association.)

surmountable directly, may require more time and ingenuity than the physician cares to give to it. In such case, absolutely no hesitation should be felt in requesting the city or state authority to supply a confidential investigator. Modern practice has achieved sufficient dependability so that no one's interest will be violated by such an intervention.

Case-holding or follow up, as has been previously pointed out, is not likely to lose in importance with any changes immediately to be anticipated

in the management of syphilis as a disease. It will be as important to follow the recipient of five-day drip or other foreshortened procedure as to hold the patient who must take sixty-five weeks of standard treatment to a tedious regimen. The same qualities that make a good contact tracer tend to make a good follow-up worker

Fig. 264.

The follow-up is controlled from the clinic by tickler calendar or by the central tabulating system which warns specifically that given individual has lapsed treatment. The very common practice of sending out letter protected by various devices against falling into the wrong hands, or non-return if undeliverable, is the least satisfactory of all effort of this kind. It usually brings return of not more than 10 per cent of the lapsers. The problem of false address, always difficult to meet, may be approached by mailing letter to the individual on the day he gives the address,

and then attempting t straighten out the false address muddle if the letter is returned unclaimed, before the patient disappears completely Where a tickler reminder fails to provoke a response, a more personal letter may follow perhaps more peremptory in tone and then the next step must be personal visit by a follow-up worker Public health urses, as follow-up workers, are excellent, particularly in the domain of the family and visiting nursing organizations also furnish valuable aids. In the pursuit of infected individuals into the underworld, objection has been made to the use of the public health nurse, but much depends upon the characteristics of the worker, and one who can perform adequately in the contact tracing field rarely fails in case-holding. The question as to when compulsion shall be invoked to oblige the recalcitrant to return for treatment cannot be categorically answered In the verage clinic, according to Ingraham's study of the problem, 70 t 90 per cent of patients disappear within a year Adequate instruction of the average new patient, as to the public health implications of his disease, is capable of improving clinic attendance only about 5 per cent. An active follow-up service ith threat of compulsion when necessary and the occasional pplication of the teeth of the law to bite the recalcitrant offender is capable of holding 70 per cent of the early infectious cases for the required period of time. Colored patients conform t treatment standards much less readily than the white. The hit man is the most susceptible t obligatory treatment methods, the colored man and woman next, and the white woman least of all.

The employment of the public health nurse in this field has been supplemented during the inadequacies of the present war by the so-called male investigator an advanced type of contact tracer often with an exceptional preparation, who is capable of organizing a considerable field, developing n acquaintance with an entire state problem and pursuing individuals not only ver the network of his own state but into surrounding states and over the country at large Such individuals are particularly important when large bodies of the population, military and civil, are on the move as in World War II, nd there are reasons to believe they should form part of the permanent venereologic establishment.

The community resources vailable for contact-tracing and case-holding are numerous and complex, nd are enumerated below The practicing physician who senses the need for study of other members of the family for example, may appeal to another physician who knows the family better than he does, but when the investigation gets beyond this point, he is wisest to ask his city or state health authority for the assistance of confidential investigator

Study and Control of the Carrier and the Reservoir.—Much of this material falls under the control of prostitution dealt ith below The question as to just how far the health officer shall go in his study of conditions hich create infection foci in community is difficult to say He rapidly finds himself becoming amateur and not too effectual sociologist or police officer Nonetheless, it has seemed to us essential that the public health officer have at least some acquaintance th the conditions in his terrain that create carrier foci, and that he shall map as precisely as possible and study the set-up of such foci. I cities in hich segregated districts do or have existed the location of clinics and prophylactic facilities often depends on an intimate survey of such conditions. The health department should therefore not leave holly to the police its knowledge of the hereabouts of distributors of disease, and should not too readily accept the st tement made by the police authority that all is quiet on the Western front. Nothing assists more to comprehension of the focal distribution of carriers nd reservoirs than does the action of ell coordinated contact tracing group which quickly demonstrates not only the center from hich trouble is coming, but the infinite network over which it flows into the community t large (see Figs. 883 and 884)

THE USE OF COOPERATING AGENCIES AND RESOURCES

The Enforcement and Probation Authorities.—The relation of public health practice to the law has long been a bone of contention. What one might call the old-line health officer repudiates vigorously any idea that he should assume responsibility for or even have guilty knowledge of the legal borderland of his terrain Nonetheless it is inescapably true that many of the most effective workers in the public health field have had almost an intimate knowledge of the functioning of law and court in an harmonious relationship with the health authority Reference has already been made to the necessity for such an understanding in the enforcement of the newer types of law (p. 1211) One of the justifiable reasons why even those health officers who have had guilty knowledge of law enforcement are showing a disposition to retreat from

the idea of participation has been the growing observable tendency on the part of the courts to absorb the functions of medical judgment in deciding whether or not a person accused of crime or sex delinquency shall be held for having or being suspected of having a venereal disease. This substitution of a medical for a legal basis of decision has several disadvantages, chief among which is the disposition to discharge all undoubted prostitutes and *ipso facto* disseminators of venereal disease from custody (isolation) upon a negative medical examination report. The venereal disease control officer especially in times of emergency like the present, may justly contend that a prostitute should be convicted for the legal crime of prostitution and detained accordingly leaving the question of the significance of her positive or negative medical findings wholly to the health authority With the incertitude attaching to negative serologic tests and negative smear examinations for gonorrhea, it is easy to understand the necessity for this contention. The court should stick to the law the health officer to the medicine.

In order to clarify to the law enforcement group the present situation with reference to venereal disease, a summary of some new and old principles was presented by Stokes (Ven. Dis. Inform. 23:303 November 1942) These are incorporated in the following summary and will serve as a practical basis of discussion for those physicians and health officers who are expanding their contacts with the enforcement authorities.

WHAT A LAW ENFORCEMENT GROUP SHOULD KNOW ABOUT VENEREAL DISEASES

A Summary of Some New and Old Principles

1 Emphasis should be shifted from "prostitution (solicitation and price) to promiscuity in sexual relations, as the basis at law of enforcement procedure. How does the law under which you work define the potential transmitter of VD as one whose sex is "for sale or one who is merely promiscuous The latter legal definition of "prostitute is closer to what you want.

2. Changing times have brought changing customs. Electricity gasoline, and rubber have dressed Venus in new clothes, provided whole new court and retinue. The telephone, the automobile, the taxicab, trailer and bus lines to everywhere; modern business organization from hot spot to card catalogue, to call girl, to chain service, city to city have promoted accessibility elusiveness, and concealment. The condom index (inspect the dooryards and pavements in the morning) in apartment house districts must now be studied rather than the count of doors in the out-dated "red-light district. The drugstore booth, pinball and telephone service and their patrons, the dog-walkers, cruising cars and convention get togethers quite as much as the bars, the taverns, clubs, hotel lobbies and bus terminals, need surveillance.

3. The purveying of sexual pleasure used to be professional specialty The hip flask, the automobile, and the scarification of young and old during and since "prohibition, have made it amateur sport. Under the emotional tensions of war the players become innumerable, and women especially may abandon themselves to relations under cloak of duty good-will, "last fling that put the enforcement mechanism y out on the edge of the problem. The girl-friend becomes anyone, anywhere, out for good time. The zipper the simplification of clothing, the car the tourist camp, the invariable presence of alcohol—the ounce too much—has spread the transmission of the venereal diseases all over the place. The gas and rubber shortage is actually card in law enforcement hand.

4 Today the field or generalized formula of VD control problem presents the following elements:

( ) Youth—desired, desiring emotional, unstable, mobile and unattached, roving, financially without stake or resource. VD is youth problem. The younger the carrier and the younger the infection, the more dangerous. The "boiled owls are more apt to be harmless.

(b) A get-together contact or dating mechanism, by which boy meets girl—e.g school, club, phone, park, dance, taproom, local groups in neighborhood contacts, job and work contacts, eating, boarding and rooming contacts.

( ) A brake-remover—usually alcohol, playing the unvarying and monotonous prelude to venery

(d) A place to do it. Where shall we draw the line? Where the lights are more than 50 feet apart, up the elevator shaft of the hotel five miles out on the state highway between the servant's bedroom on the top floor and the living quarters?

5. As a problem (and it is always a local one) is tested or analyzed by this formula it becomes clearer where the preventive or controlling emphasis must be placed, and the agencies that must be called on to deal with each subdivision. Where is youth in the picture (juvenile court, probation, the policewoman) what the get togethers how does the brake-remover enter the problem (don't forget local standards and morals) where is the place and how can it be dealt with? An all-out program deals with all.

6. Into those parts of the formula that enforcement cannot reach, the contact tracer carries the individualized confidential approach. He (or she) discovers the garage that is the rendezvous for a group of perverts who have been introduced to the spiral germ of syphilis by one infected member—the five families in one blind alley stirred into a venereal omelet—and so on.

7. Well-considered experience indicates that the health department or officer through the stories obtained from patients in the clinics to which year in and year out they go for treatment, uncovers from 20 to 40 times as many sources or carriers of venereal disease as does the examining mechanism associated with the courts. Nothing shows more clearly that prostitution is no longer, if it ever was, the principal commercialized source of venereal infection. Nothing shows better the need for close cooperation between courts and health departments in the effort to control the spread of disease. The contact tracer can usually add new infection carrying links, even to a court chain, in persons never brought to the attention of the law.

8. Every infectious case, every person complained of as a source of infection whose identity can be secured in an enforcement procedure, is a priceless lead to the VD control officer in following up the trickle of infection, the secret rills of disease transmission that never come to enforcement notice. No greater service can be rendered public health than for the court and police authorities to keep the contact tracer and his Health Department VD chief always in mind, always at their elbows, constantly informed and utilized. They will do their work confidentially and well.

A second important field of public health and enforcement contact, is that concerned with the bringing in of suspects for examination. Reference has already been made to the use of almost extrajudicial procedure in emergency conditions, to bring in from all directions, possible disseminators of venereal disease, particularly women and young girls. Justification for the use of devices like the loiterers statute and the curfew enactment is found in the undoubted shift of promiscuity in sexual relations from the professional of old-line prostitution to the amateurs of the modern joy-ride. Here again, the principle of rigorously applied scrutiny in behalf of human civil liberties deserves consideration, and judges who are sensitive to it not infrequently incur the disapproval of other agencies in the protective and preventive field which desire to extend the examination of suspects to its widest limits.

A device which bears an almost surely emergency stamp is examination on complaint. This procedure reluctantly accepted in tracing contacts among the armed forces, has not reached the point thus far in the United States where fewer than three witnesses to the identity of the source of infection is sufficient to force examination. In Great Britain however a, for the British, truly astonishing structure upon the rights of the individual, has been promulgated in Regulation 33-B, added to the General Defense Regulations of 1939. This regulation requires that any physician treating a patient with venereal disease must fill out an appropriate form concerning the suspected source of infection and this complaint been repeated by a second person permits the medical officer of health to conduct a physical and laboratory examination of the accused, under compulsion if necessary. The efficacy of this regulation as teeth has been greatly hampered if not largely nullified by the fact that the infected person is required to name not his sexual contact, but the person from whom he believes the infection to have been acquired, and heavy penalties are attached to false accusation when demonstrable. This, of course drives all information into hiding at once.

The Council of Social Agencies.—This, or its equivalent, is part of the social service organization of practically all large cities, and serves as the coordinating center for a variety of aids which the health department may invoke. It is, however in the main a policy-determining educational and social service exchange type of group whose support should be enlisted but active

utilization of its components can only be obtained by direct personal approach.

The visiting nurse is of especial service in establishing family contacts, and in organized care of the pregnant woman, with respect to venereal disease. She should especially be schooled to the principle that syphilis in the pregnant woman does not end for either her or the child with the mere fact of delivery or discharge from the maternity hospital. The visiting (*i.e.*, public health) nurse should be familiar enough with the course of syphilis; have seen some of its infectious lesions; have an index of suspicion with reference to blindness, cardiovascular disease, and neurosyphilitic manifestations, and be familiar with the requirements of the law with regard to prenatal and premarital blood-testing. Th school medical authority and with it, the school nurse, usually comes into direct contact with syphilis through the occurrence of acquired infections in young persons, hich are commoner than is often supposed; congenital infection, manifested in interstitial keratitis especially; and sex delinquency with its risk of venereal disease transmission manifested in illegitimate pregnancy The schools further bear an important part, more it must be conceded, in prospects for the future, than in present achievement, in the morale and educational front of venereal disease control. Especially appointed school counselors, high school principals, and the physical education instructional staff have particularly good opportunity to deal with juvenile transmission problems. Th family nd maternal child health societies have titulary interest in syphilis and its control and may be enlisted if they have active health centers or clinic establishments. Family clinics are valuable segregative division of venereal disease and have valuable segregative function within the general syphilis clinic. A mother with young child is demonstrably far more willing to accept treatment herself, and carry through for her children, when one visit will take care of both.

Th pharmaceutical associations and the pharmaceutical profession hold key position in the front against venereal disease. The drugstore is often the social center of neighborhood; it is often a gathering place and refreshment spot for young people at the age when the start towards venereal disease is most often made. The socially-minded head and personnel of such establishments can (*a*) discourage off color frequenters looking for pick-ups and trouble; (*b*) give friendly advice and even sober counsel to some who are obviously on the way to going wrong; (*c*) urge blood tests and medical examinations on persons who are known to have exposed themselves. The pharmacist can, if he will, maintain center for public health and preventive medicine, comparable in some ways even to the physician office. From behind the counter he has the first chance to give or sell prevention to the person who may be exposed to venereal disease. H can be sure that the prophylactic or the kit is top-grade approved product. He can emphasize the importance of time in postexposure prophylaxis, and warn the victim of "the ounce too much, of the need for immediate action. The pharmacist above all can sell the basic idea of prompt, accurate diagnosis and immediat treatment to the person who describes the symptoms or asks for treatment or relief; the person who asks for or purchases proprietary for venereal disease treatment *tells the story that shows he is taking risks he doesn't realize*; has consulted quack; or has no medical care. If the physician interested in venereal disease control will establish reciprocal contacts ith the pharmacist, he will find him much more cooperatively minded, than if the arrangement is only expected to work one way—from the drugstore to the doctor office.

The medical societies and specifically the county and state associations, have shown wide regional variation in their responsiveness to the responsibility for venereal disease control. Where public health practice was popular as ith the profession in Detroit, under the leadership of Henry Vaughan, the practicing physician was one of the most eager of cooperators, and his county society fully reflected his attitude. In certain states and municipalities the schism between medical society and public health authority has not progressed beyond stolid refusal to cooperate, on the one hand, and indignant sputterings on the other In fortunately limited number of instances, the medical society has placed an active lobby in the stat legislature to block free diagnosis and to see that free treatment is given to none but the indigent. It has even appeared that the profession, through carelessness, no doubt, has on the one hand, utilized the free diagnostic service of the premarital examination la n, to secure free blood-tests for patients nd been willing to certify them as indigent while charging for the certificate. Broadly speaking, it may be said that the profession either has nothing to lose by an increased assumption of responsibility by the health authority or can expect positive gains therefrom. For example, the institution of mass blood-testing has demonstrably in certain cities in this country increased, nd to striking degree, the privat practice of physicians willing to treat venereal disease. This is the usual rule. There is more tha enough for all, if all is uncovered. Generally speaking, the health authority should at the earliest possible moment, and consistently and repeatedly thereafter seek the counsel of the local medical society take it into his counsels preserve personalized and intimate

rather than a distant high and mighty approach to the individual practitioner and in every possible way convince the everyday doctor that he is a vital element in the control of syphilis.

The American Social Hygiene Association has supplied a generous share of the initiative in venereal disease control, particularly in its relation to social hygiene and the war effort. The national association has a number of local chartered branches, and through its central organization will supply ideas, educational material, cooperative liaison, with national groups such as pharmacists, and investigative services, particularly in the law-enforcement field which are an important part of civilian or private initiative in venereal disease control problems. If the health authority genuinely desires participation of all the people in the solution of what is all their problem, it will utilize and strengthen the voluntary agencies of this type in venereal disease control.

THE PREVENTION OF THE VENEREAL DISEASES

Fundamental Principles.—In May 1942 all vehicles of the Philadelphia Transportation Company including streetcars, buses, subway cars and trains and trackless trolleys, carried in behalf of the City Defense Council's Venereal Disease Subcommittee an advertisement which epitomizes the principles of prevention of venereal disease. This card is reproduced in Fig. 885 An alert

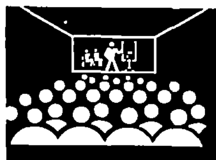


Fig 885 —Street Car Advertisement—see text.

observer will note the one omission—public education—of one aspect of which the card itself was an exemplification.

The Morale Front.—*The British Army Bureau of Current Affairs* in its Handbook revision for 1943 supplies what might well be quoted as the Magna Charta of the morale front "Morale depends on knowledge There is a widespread ignorance among soldiers about current affairs an ignorance not peculiar to soldiers, but a chronic condition among the citizens of this country An ill informed or indifferent citizen or soldier is a menace to national safety Morale is a matter of discipline which in turn, is a function of understanding. It is not enough to apply these principles to military matters only the citizen-soldier should realize Cromwell's definition of one who must know what he fights for and love what he knows.

The car advertisement purposely placed clean living clean sport and recreation first under the controlling influences, in the belief that the summated experience of a century has clearly shown that the positive moral force of a people or a community and the agencies which encourage it are the groundwork of that self-control which controls the venereal diseases. Sexual misconduct

duct begins at the point where the individual, lacking inspiration to clean living and with excess energy and money to spend, follows the aberrant track of an emotion uncontrolled by intelligence to an unsound solution of a basic need. The basic need being inescapable, and variable in its intensity from individual to individual, the classification of influences leading to the undesirable solution will be difficult, but fortunately the classification of the influences restraining him will be relatively simpler Granted that the hereditary background and childhood associations and experience are not too prejudicial (and these are large grants) the majority of human beings will (*a*) work out a not too discreditable solution of the individual sex problem by the end of adolescence and (*b*) if given sufficient play to offset worry and sufficient hard physical work to discharge tension, will be able to employ reason and ideals in meeting an impulse to sexual indulgence. It follows therefore, that to control loneliness and homesickness, to provide adequate substitutes for temporarily severed human associational ties, especially with the other sex· to provide a cause, ideal or aim which validates effort and assures the future and to keep the individual working hard towards it, will tend to reduce the morale problem of sex conduct to the most controllable terms.

In World War I, for wars are always crises in these affairs, it has been pointed out that the compensatory forces got under way early· in the Commission on Training Camp Activities they had full encouragement and support, and the influence of the American Social Hygiene Association, and General Pershing uncompromising stand on the matter made real what might otherwise simply have remained paper.

The generation between the first war and the second has seen number of important changes —perhaps one might almost say leaks or breaches in the morale front. The experiment of prohibition unenforced, simultaneously with the advent of the automobile, put youth to test in which its morale survival values are not yet established. Delays in bringing to bear some of the control influences early evolved in the last war have doubtless influenced an early unfavorable trend in venereal disease incidence both in civil and military life. But far more important are the serious elements of difference in the morale problem of this war as compared with the last. Scientific discoveries may and in fact are already enhancing the effect of general loosening up of sex standards. As evidence of the loosening, we witness shift of the infection source from professional prostitute to casual amateur which has delayed and even defeated the approach to control at number of important points (see below). W find the girl-friend or pick-up performing her uncertain offices without cost, which confounds the police ttack on prostitution, and we find among omen and girls of the most unexpected types an almost vid desire to show the boys good time. Solicitation seems to be climbing to unheard-of proportions in many cities, and in other countries as well as our own, and the dating mechanism developed during peace is superfunctioning in time of ar Some peculiarities of our national effort are important too. W are concentrating troops overwhelmingly in the South in areas where both white and colored races have phenomenally high incidence of venereal disease. The color-line is thinning, drawing on the Negro reservoir of infection, the highest in the country Transportation has done things to peripheral cantonment control which worked in the last war but is far less effective in this. The population as well as the armed forces is on the move, and civilian equally with the soldier and sailor is swept into the morale-wrecking effects of change, break-up of home and stabilizing influences, loneliness, unrest. Liquor has been less effectively dealt with later in the game than in the last war And now scientific discovery—the one-day cure of the maligned but often effective fear-producing deterrent of disease—is knocking out the props from under our platform.

It may then well be asked where shall turn, in situation like this, if not to the rediscovery of old truths and their reemphasis in education. The scanty grace now accorded clean way of living; continence dismissed in five words followed by "but, in the current official instructional films—only impresses the more intensely the need, the imperative need for moral rejuvenative and positive force t replace growing cynicism in this whole business. Perhaps it is intended to leave all that to the chaplains. Earnest and effortful though they may be, they will fail. The control of venereal disease, the clean conduct of the sexual life cannot be made effective by ecclesiastically coated pills. It is man-to-man and day-to-day affair. In civil life its exponents should be the parents who are the living examples; the teacher who is too often perforce the official in-

structor In the armed forces, it is the business of the commanding personnel from squad corporal to colonel and general on the land, and up the Navy's staff to the top-most admiral on the sea. The attitude of the physician, more important by far than he may realize, should be uncompromising. The medical officer in particular owes the morale side of this problem an unbrisking and wholehearted allegiance.

The man on whom it fell to summarize the record of the American Expeditionary Forces in the last war is not too incorrectly quoted as saying that the sense of being set apart for a great destiny raised the proportion of continence in our Army far above the expectancy for armies in general and that continence and not the barbed wire of St. Nazaire kept down our rates. This being set apart for a great destiny belongs not alone to the heroic moments of life, but to the everyday drudgery of living. As such, it must be made a part of the fabric of our being, and the venereal disease control officer must insist that this is so. Of the here and now it may truthfully be said that if ever there was a day when the bodies of men, equally with their souls, are set apart for great destiny this day is it.

Education.—It has been indicated that much educational effort in the prevention of venereal disease falls under the condemnation of Ecclesiastes—of the making of many books there is no end and much study is a weariness let us hear the conclusion of the whole matter Fear God, and keep His Commandments Education is a supplement and elaboration of example example begins in the home and is merely carried forward by the school and all those forces and agencies which under the guise of organized play and association try to make the square deal and the do unto others the basis of behavior Precisely as it has become clear in the educational effort among soldiers and sailors that the small group the eye-to-eye talk, the vivid and dramatic instructional episode iterated and reiterated time after time finally teaches something so it appears the more intimate and direct approaches in preventive educational technic at large may be expected to be the most effectual Such education is not successfully carried through by the inexperienced or by all who may feel the urge to attempt it. Accordingly along with sound general direction, educational programs require specialized and again adept personalities to carry their message across.

This type requisite has stood out of all the varieties of educational experiment that have marked the past twenty-five years in schools, YMCA s and other groups Much of the reluctance which has been apparent to transfer sex education to the school as against the home has been based on the contention that the contact cannot be so intimate, the example is less clear the precept more formal and potentially embarrassing and the teacher too often himself an unadjusted individual unfit either as an example or an instructional agent. Despite these strictures on sex education in the schools, it has become increasingly apparent that something in this field must be invoked to head off the increasing trend toward juvenile promiscuity

The earlier conceptions of sex education tended either to etherealize on generalities or to specialize in prophylactic frankness Special situations may of course require the latter but the general situation now appears to require first, an integration of instruction in matters of sex with the general content of instruction in health and hygiene at large Second, the range of such instructional effort has been extended from the original application to the teen-age high school group, to the parents, even the prenatal parent so to speak, and the child from infancy to and through the college years. Thus sex education becomes in the term applied to the preparatory instructional course for teachers and counselors given in 1913 by the Institute for the Control of Syphilis at the University of Pennsylvania a course in "Health and Human Relations." A third principle is that of central full-time guidance for the program wherever and however instituted in the school system A fourth calls for the utilization and preparatory instruction of persons of special aptitude from the teaching staff itself This includes school counselors, school principals, instructors in physical education and others who have demonstrated special capacity for dealing effectively with the problems of youth.

Special information on the educational plans of the Philadelphia School System and the curriculum of the course in Health and Human Relations for counselors and teachers may be obtained from the Board of Education, 21st and the Parkway Philadelphia, or the Institute for the Control of Syphilis, Hospital of the University of Pennsylvania.

A surprisingly large part of educational effort in this field at the present time is represented by the moving picture. Typical and worth while films include "Know for Sure" (United States Public Health Service), "In Defense of the Nation" (American Social Hygiene Association) and the various instructional films of the Army and Navy. In our opinion these are essentially stop-gap devices, creditable though several of them are, to meet special situations in what must ultimately be a broadly organized program. They are under fire of criticism from groups in the church which believe that they underestimate, if they do not actually damn with faint praise the morale aspects of venereal disease control. Certainly one feels this lack in the instructional films used by the armed forces in the early part of this war, and in some of the franker pamphlet literature, especially on prophylaxis, which has had high and wide sponsorship and circulation.

The question of reading matter for educational purposes is often referred to the physician. A particularly good summary of the worth while social hygiene books and pamphlets, and the function and equipment of the public library with reference to sex education, is given in the *Journal of Social Hygiene*, volume 29, June, 1943. Excerpts from this material and advice on these problems may be obtained from the American Social Hygiene Association, 1790 Broadway, New York, and the United States Public Health Service Division of Venereal Diseases, Bethesda Station, Washington, 14, D. C. It is necessary to remark that the educational front of venereal disease control has as deep a lunatic fringe as any in the calendar. By no means all who feel themselves called, should be chosen to the business of inspiring and educating the public in this field particularly. The health officer should scrutinize; the physician should gravely question each and every one called to missionary effort lest he find himself and his program encumbered by deluded crank.

The Control of Organized Prostitution.—Organized vice or prostitution has so long held the center of the stage in venereal disease control thinking that it requires a basic analysis, even though it seems in the process, for the present war at least, of being displaced as the major infectious source by the nonprofessional promiscuous individual. In a considered statement, the Subcommittee on Venereal Disease Control of the Philadelphia Defense Council and the Pennsylvania State Venereal Disease Control Committee laid the present situation with reference to prostitution before its public, and this statement seems worth quoting in full.

A STATEMENT ON PROSTITUTION

Two schools of practice have existed since the beginning—segregation and tolerance or repression.

As medicine progressed it added the notion of safety to the segregation, by inspection.

As medicine progressed a little further it found inspection unreliable because of difficulties in diagnosis and uncertainty as to continuity of the negative or disease-free status. This is the still unsolved carrier problem, active and passive.

As it progressed still another step, it proposed to keep the infected or infectable individual free of infectious lesions by chronic treatment, so to speak. The bismuth plug, the periodic sulfonamidization are examples of this technic.

Meanwhile science had stepped in from another angle and proposed the local use of antigonococcal and antispirochetal disinfectants plus devices for keeping infective organisms away from susceptible and exposed parts—in other words, post and preexposure prophylaxis.

The latest contribution is that of epidemiology—the art and science of the contact tracer.

Study of contact tracing results and the sex habits of infected persons seems to show that:

1. *Most males and many females* have worked out some individual sex solution or compromise by early adulthood, either continence, masturbation or one or another kind of sexual relation. A relatively small proportion are inactive. The Army's impression seems to be: 15 to 20 per cent won't, 15 per cent will, 70 per cent shift back and forth under the influence of this or that circumstance including upbringing, availability, companionship, mass or group morale, work interest and fatigue, normal recreation and distraction, feeding, and above all, alcohol. It is to be expected therefore, that the soldier or sailor viewed realistically will have a sex life subject to these influences and influenced by what we do about them.

2. *The old symbolic concept of prostitution* as organized house and solicitation activity gov

Colonel Ashburn at the close of the last war (1919) estimated that 30 per cent of the A.E.F. remained absolutely continent during their service in France.

varying facilities for sexual intercourse with the shift from professional to amateur. This makes doubly important the emphasis which Williams, who has a singularly effective record in the clean-up of Vancouver and the seaport towns of British Columbia, puts on the suppression of what he calls the "facilitator" as distinguished from the woman victim of the prostitution situation. The beginning of an attack on facilitating agencies is in an adequate contact tracing technic. The aim is to find the place at which the exposure occurred and then to trace the place to its ownership, and to persuade the ownership to active cooperation in extinguishing the place. Such efforts, of course, bring contacts with other facilitative agencies including the distributors of alcohol, the call mechanism for summoning girls, and so forth. The emphasis on the place is, of course, longstanding prostitution control practice, but Williams' emphasis on the person as distinguished from the legalist approach, is new. The attack on the facilitator is emphasized in the foregoing summary of prostitution control by the italicized items 7 to 10 inclusive, under "How Can Prostitution Be Repressed."

Appreciat[illegible] of the horrible example, particularly under American conditions, Parran and V[illegible] Words about Venereal Disease, Reynal and Hitchcock, [illegible] tersel[illegible] representative of segregationism and prost[illegible] from [illegible] California, city with a normal population of 14,000, [illegible] at the beginning of 1941. Thousands of troops [illegible] the cities of Monterey, Salinas, and other [illegible] entertainment for the boys. The prost[illegible] regulated houses. [illegible] visited the cribs by the hundreds, that the Army [illegible] out-of-bounds. It was easy to take this action [illegible] rors, and kept what they made after they paid [illegible] th for a wooden shack divided into a bedroom [illegible] cks constituted the crib area. The bedroom [illegible] manpower paraded past while the girls sat in their [illegible] ve customers might get a good look at them. [illegible] ted area of Salinas. Half a dozen houses [illegible] an adjacent side street. Several houses were [illegible] remodeled while occupied. The Madame [illegible] ng that she had twelve nice girls, was increasing her [illegible] ing equipment, and expected to have the [illegible] finished. If the Army camps nearby continued [illegible] girls if necessary. The segregated area of Salinas [illegible] represents so-called "effective segregation" [illegible] tion of the venereal disease problem. It is [illegible] town for the Army in early 1941 was in an [illegible] alled the apparatus for what may have been a [illegible] f the exposed man would walk through the [illegible]

Wh[illegible] of the horrible examples citable today will be cleaned up [illegible] yesterday there is no escaping the fact that similar "solutions" [illegible] time in any place in the country or the [illegible] the indifference or cynicism of the medical [illegible] and line officers, encourage them.

Alcohol [illegible] the Siamese twin of venery and no operation has been [illegible] can separate the two without the death of the one or disappearance of the other. A distinguished medical officer expressed [illegible] aphoristically — Only to a drunk does a whore look good. [illegible] of the influence of commercialized liquor on prostitution [illegible] stuff buried in papers of the preprohibition era, among them Kneeland's [illegible] cal study (Social Hygiene 1916 volume II 69–90) and Clark ([illegible] 3:75–90). From 50 to 80 per cent of exposures by various estimates [illegible] under the influence of alcohol and it has been sourly remarked by [illegible] in charge of a huge prophylactic station that a man must be [illegible] to submit to prophylaxis. It is quoted as axiomatic that prophylaxis should be so placed that a drunk will not walk uphill. Under [illegible]

A surprisingly large part of educational effort in this field at the present time is represented by the moving picture Typical and worth while films include "Know for Sure (United States Public Health Service) "In Defense of the Nation (American Social Hygiene Association) and the various instructional films of the Army and Navy In our opinion these are essentially stop-gap devices, creditable though several of them are, to meet special situations in what must ultimately be broadly organized program They are under fire of criticism from groups in the church which believe that they underestimate if they do not actually damn with faint praise the morale aspects of venereal disease control. Certainly one feels this lack in the instructional films used by the armed forces in the early part of this war, and in some of the franker pamphlet literature, especially on prophylaxis, which has had high and wide sponsorship and circulation.

The question of reading matter for educational purposes is often referred to the physician. A particularly good summary of the worth while social hygiene books and pamphlets, and the function and equipment of the public library with reference to sex education, is given in the Journal of Social Hygiene, volume 29 June, 1943. Excerpts from this material and advice on these problems may be obtained from the American Social Hygiene Association, 1790 Broadway New York, and the United States Public Health Service Division of Venereal Diseases, Bethesda Station, Washington, 14, D C. It is necessary to remark that the educational front of venereal disease control has as deep lunatic fringe as any in the calendar By no means all who feel themselves called, should be chosen to the business of inspiring and educating the public in this field particularly The health officer should scrutinize the physician should gravely question each and every one called to missionary effort lest he find himself and his program encumbered by deluded crank.

The Control of Organized Prostitution.—Organized vice or prostitution has so long held the center of the stage in venereal disease control thinking that it requires a basic analysis, even though it seems in the process, for the present war at least, of being displaced as the major infectious source by the nonprofessional promiscuous individual. In a considered statement, the Subcommittee on Venereal Disease Control of the Philadelphia Defense Council and the Pennsylvania State Venereal Disease Control Committee laid the present situation with reference to prostitution before its public, and this statement seems worth quoting in full.

A STATEMENT ON PROSTITUTION

Two schools of practice have existed since the beginning—segregation and tolerance or repression.

As medicine progressed it added the notion of safety to the segregation, by inspection.

As medicine progressed little further it found inspection unreliable because of difficulties in diagnosis and uncertainty as to continuity of the negative or disease-free status. This is the still unsolved carrier problem, active and passive.

As it progressed still another step, it proposed to keep the infected or infectable individual free of infectious lesions by chronic treatment, so to speak. The bismuth plug, the periodic sulfonamidization are examples of this technic.

Meanwhile science had stepped in from another angle and proposed the local use of antigonococcal and antispirochetal disinfectants plus devices for keeping infective organisms away from susceptible and exposed parts—in other words, post and preexposure prophylaxis.

The latest contribution is that of epidemiology—the art and science of the contact tracer Study of contact tracing results and the sex habits of infected persons seems to show that

1 *Most males and many females have worked out some individual sex solution or compromise* by early adulthood, either continence, masturbation or one or another kind of sexual relation. A relatively small proportion are inactive. The Army impression seems to be: 15 to 30 per cent won't, 15 per cent will, 70 per cent shift back and forth under the influence of this or that circumstance including upbringing, availability companionship, mass or group morale work interest and fatigue, normal recreation and distraction, feeding, and above all, alcohol. It is to be expected therefore, that the soldier or sailor, viewed realistically will have sex life subject to these influences and influenced by what we do about them.

2. *The old symbolic concept of prostitution* as organized house and solicitation activity gov-

Colonel Ashburn at the close of the last war (1919) estimated that 30 per cent of the A.E.F remained absolutely continent during their service in France.

tractor. In the armed forces, it is the business of the commanding personnel from squad corporal to colonel and general on the land, and up the Navy staff to the top-most admiral on the sea. The attitude of the physician, more important by far than he may realize, should be uncompromising. The medical officer in particular owes the morale side of this problem an unshrinking and wholehearted allegiance.

The man on whom it fell to summarize the record of the American Expeditionary Forces in the last war is not too incorrectly quoted as saying that the sense of being set apart for a great destiny raised the proportion of continence in our Army far above the expectancy for armies in general, and that continence and not the barbed wire of St. Nazaire kept down our rates. This being set apart for a great destiny belongs not alone to the heroic moments of life, but to the every day drudgery of living. As such, it must be made a part of the fabric of our being, and the venereal disease control officer must insist that this is so. Of the here and now it may truthfully be said that if ever there was a day when the bodies of men, equally with their souls, are set apart for a great destiny, this day is it.

Education.—It has been indicated that much educational effort in the prevention of venereal disease falls under the condemnation of Ecclesiastes—"of the making of many books there is no end, and much study is a weariness ... let us hear the conclusion of the whole matter: Fear God, and keep His Commandments." Education is a supplement and elaboration of example; example begins in the home, and is merely carried forward by the school and all those forces and agencies which under the guise of organized play and association try to make the square deal and the "do unto others" the basis of behavior. Precisely as it has become clear in the educational effort among soldiers and sailors that the small group, the eye-to-eye talk, the vivid and dramatic instructional episode iterated and reiterated time after time finally teaches something, so it appears the more intimate and direct approaches in preventive educational technic at large may be expected to be the most effectual. Such education is not successfully carried through by the inexperienced or by all who may feel the urge to attempt it. Accordingly, along with sound general direction, educational programs require specialized and again adept personalities to carry their message across.

This type requisite has stood out of all the varieties of educational experiment that have marked the past twenty-five years in schools, YMCA, and other groups. Much of the reluctance which has been apparent to transfer sex education to the school as against the home has been based on the contention that the contact cannot be so intimate, the example is less clear, the precept more formal and potentially embarrassing, and the teacher too often himself an unadjusted individual unfit either as an example or an instructional agent. Despite these strictures on sex education in the schools, it has become increasingly apparent that something in this field must be invoked to head off the increasing trend toward juvenile promiscuity.

The earlier conceptions of sex education tended either to etherealize on generalities or to specialize in prophylactic frankness. Special situations may of course require the latter, but the general situation now appears to require, first, an integration of instruction in matters of sex with the general content of instruction in health and hygiene at large. Second, the range of such instructional effort has been extended from the original application to the teen-age high school group to the parents, even the prenatal parent so to speak, and the child from infancy to and through the college years. Thus sex education becomes in the terms applied to the preparatory instructional course for teachers and counselors given in 1935 by the Institute for the Control of Syphilis at the University of Pennsylvania, a course in "Health and Human Relations." A third principle is that of central full-time guidance for the program wherever and whenever instructional in the school system. A fourth calls for the utilization and preparatory instruction of persons of special aptitude from the teaching staff itself. This includes school counselors, school principals, instructors in physical education and others who have demonstrated special capacity for dealing effectively with the problems of youth.

Special information on the educational plans of the Philadelphia School System and the curriculum of the course in Health and Human Relations for counselors and teachers may be obtained from the Board of Education, 21st and the Parkway, Philadelphia, or the Institute for the Control of Syphilis, Hospital of the University of Pennsylvania.

8. *From the owners of property* used for prostitute and affiliated activity or their estat representative—the "vested interests.

9 *From all sorts of persons and sources who believe*

( ) That stopping prostitution leads to increase in rape.

(*b*) That the sole or chief source of disease is the "institution of prostitution and the "prostitute, who can be caught, confined, controlled, inspected, treated—forgetting all the other sources mentioned.

(*c*) That repressing prostitutes drives them into hiding and scattering—forgetting that this very thing enormously decreases their accessibility and contact frequency—especially to soldiers and sailors, who as strangers, if looking for sex, strike out for the sex district if there is one.

What happens when prostitution, in the institutional or house sense, is vigorously and effectively repressed? There are some recent excellent demonstrations—a notable one in the Pacific Northwest, Washington and British Columbia for example.

1 *Gonorrhea* is often greatly reduced in incidence almost at once.

2. *Syphilis is less rapidly influenced*, for unknown reasons, but possibly because more of the syphilis of the established prostitute (this does not mean merely blood-test syphilis or latency) is past the infectious stage or controlled by treatment. The "prostitute is less dangerous source of syphilis often than the casual" and the ignorant but promiscuous "girl friend.

3. *The house of ill fame* is broken up as criminal resort and hide-out with corresponding improvement in the criminal and liquor control situations.

How can prostitution be repressed and infective exposure of all sorts reduced to the lowest terms?

1 *By developing an uncompromising public demand for clean-up.* A process of education.

2. *By all-out medical acceptance* and endorsement of the epidemiologic facts and the viewpoint on which repression is based (see above).

3. *By punishment*, legal and otherwise, of violators of the health regulations regarding inspection and certification of prostitutes if such regulations exist in the statutes of the state or municipality If no law against inspection and certification exists, let the community or state be persuaded by the physicians to get one.

4. *By as wide an application of the examination of males and females* caught in the toils as local sentiment and law permits—release to probation on positive findings to include treatment and follow-up of infected persons.

5 *By long-term imprisonment* (not fines) of the repeatedly convicted prostitute, imprisonment meaning commitment to an institution where ( ) adequate treatment carried to cure is given (not the average thirty-day county jail sentence) and (*b*) probationary rehabilitation placement work is effectively carried out.

6. *By invoking the May Act* through the military or naval authorities if the exposure of soldiers and sailors is an important element in the situation, and local inertia blocks action.

7 *By "padlock" law*, closing properties rented for or by prostitution or its agents, to all uses for year or more.

8. *By publicizing recalcitrant and reactionary conduct or noncooperation*, on the part of all agencies such as hotels, and hot-spots, real estate owners and agents, liquor dispensers (taverns, etc.) frequented or used by prostitutes.

9 *By cleaning up the police administration* if corrupt.

10. *By starting an FBI investigation* of the "higher-ups via the income tax, where officially tolerated corruption exists.

11. *By cooperating with the armed forces* in the identification of sources of infection in the community

12. *By establishing prophylaxis* (preventive treatment) (station, dispensing, etc.) on locally satisfactory basis, for post exposure and if possible pre-exposure technics.

13. *By enlisting the help* in controlling mobile and casual prostitution, of the following agencies:

(*a*) *The State Health Department' Division of Venereal Diseases*, whose expert contact tracers (epidemiologic workers) are trained to trace venereal disease to its source, quietly confidentially unobtrusively and to bring it under treatment.

(*b*) *The Beverage Control Board*, which can help to identify and control the alcohol factor especially by strict enforcement of the Liquor Control Act in licensed premises.

(*c*) *The automobile licensing authorities and State Highway Department* which can help control the taxicab, the parked car and the trailer

(*d*) *The State Motor Police*, usually of higher than average morale, who can help control the road house and the tourist camp and dine-and-dance.

It would be mistake to suppose that organization is disappearing from the business of pur

varying facilities for sexual intercourse with the shift from professional to amateur This makes doubly important the emphasis which Williams, who has a singularly effective record in the clean-up of Vancouver and the seaport towns of British Columbia, puts on the suppression of what he calls the "facilitator" as distinguished from the woman victim of the prostitution racket. The beginning of an attack on facilitating agencies is in an adequate contact tracing staff and technic. The aim is to find the place at which the exposure occurred and then to trace the place to its ownership, and to persuade the ownership to active cooperation in extinguishing the place Such efforts, of course, bring contacts with other facilitative agencies including the distributors of alcohol, the call mechanism for summoning girls, and so forth. The emphasis on the place is, of course, longstanding prostitution control practice but Williams s emphasis on the persuasive as distinguished from the legalistic approach, is new The attack on the facilitator is emphasized in the foregoing summary of prostitution control by the italicized items 7 to 10 inclusive, under "How Can Prostitution Be Repressed.

Appreciating the force of the horrible example, particularly under American conditions, Parran and Vonderlehr (Plain Words about Venereal Disease, Reynal and Hitchcock, 1941) tersely described several situations representativ of regulationism and prostitution on the loose, from which we quote. Salinas, California, a city with normal population of 10,000, had from 200 to 300 women engaged in prostitution at the beginning of 1941 Thousands of troops are being concentrated in Monterey County nd the cities of Monterey Salinas, and other nearby towns are outdoing themselves in providing "entertainment for the boys. The prostitutes were separated in two areas, the cribs and the regulated houses.

Such disorder resulted when men visited the cribs by the hundreds, that the Army authorities found it necessary t put these places out-of-bounds. It was easy to take this action because the crib girls were free lances, had no procurors, and kept what they made after they paid the exorbitant rent of hundred dollars month for wooden shack divided into a bedroom and toilet. Seventy-five to hundred of these shacks constituted the crib area. The bedrooms opened directly on a walk-way and the military manpower paraded past while the girls sat in the brightly lighted bedrooms where the prospective customers might get good look at them. Two or three blocks way was the so-called segregated area of Salinas. Half dozen houses were on ts sides of single block and several more on an adjacent side street. Several houses were under construction and one of the oldest was being remodeled while occupied. The Madame extended a warm greeting t the investigator nnouncing that she had twelve nice girls, was increasing the number of rooms and modernizing the plumbing equipment, and expected to have the most sanitary house in the town hen the job was finished If the Army camps nearby continued to grow she expected to bring in as many as thirty girls if necessary The segregated area of Salinas is typical of many cities in the U ited States It represents so-called effective segregation in this country, which still is advocated as solution of the venereal disease problem It is significant that the only prophylactic station in the town for the Army in early 1941 wa in an alley back of the crib area in which had been installed the apparatus for what may have been well administered prophylactic treatment, if the exposed man would walk through the mud in the unpaved alley to get it.

While most of the horrible examples citable today will be cleaned up tomorrow or have been cleaned up yesterday there is no escaping the fact that similar solutions" for local venereal disease problems may arise at any time in any place in the country or the world where local public sentiment, official corruption, the indifference or cynicism of the medical profession, and the anachronistic notions of medical and line officers, encourage them.

Alcohol.—Liquor is the Siamese twin of venery and no operation has yet been devised which can separate the two without the death of the one or the disappearance of the other A distinguished medical officer expressed the situation aphoristically—'Only to a drunk does a whore look good" Knowledge of the influence of commercialized liquor on prostitution is essentially old stuff buried in papers of the preprohibition era, among them Kneeland's classical study (Social Hygiene, 1916, volume II 00–00) and Clark (*Ibid.*, 1917 3-5-00) From 30 to 80 per cent of exposures by various estimates take place under the influence of alcohol, and it has been sourly remarked by the sergeant in charge of a huge prophylactic station, that a man must be slightly drunk to submit to prophylaxis. It is quoted as axiomatic that prophylaxis stations should be so placed that "a drunk will not walk uphill" Under the ordinary

conditions of venereal disease control, the Beverage Control authority deals with the liquor factor along three lines prosecution (1) for sale to minors, (2) for keeping open beyond established hours (usually midnight or 2:00 a.m. or Sundays in some leave areas) and (3) for sale of liquor to intoxicated individuals. The law also usually intimates that bar keepers and owners are not expected to permit known prostitutes to frequent their premises, but this is extremely difficult of enforcement. Each of these provisions recognizes the principle of keeping alcohol out of the hands of inexperienced and emotionally dominated persons (youth) limiting the time of its availability to those hours when people would rather drink and sit in public than, drunken, fornicate in private. Midnight closing cuts off a considerable accession to the exposure field in the persons of those who go from bar to room on the same premises. At what point the intoxicated person reaches his maximum susceptibility to prostitute solicitation is, of course, undetermined but there is little doubt that the succumbing point gets nearer and nearer as the ingestion of alcohol increases. While the cleaning up of a wide open town or district with respect to liquor violations does not of necessity clean up the prostitution or venereal disease dissemination situation at large, a shut-down on alcoholic over-indulgence is practically always the first step in genuine reform.

Other Forms of Commercialization of Sex.—Pornography in pictures, postal cards and magazines; the "cheese cake" or photographic leg work, which is alleged to sell the nationally known illustrated magazines; and shading upward, the pulp and sexy story magazine, probably act more directly upon the adolescent than upon the older age groups in the stimulation of promiscuous activity

Prophylaxis, Mechanical and Chemical.—Prophylaxis in this sense is pre-infection or preventive treatment. It is subdivided into pre- and post-exposure categories, into personal and station prophylaxis. The indubitably tremendous effectiveness of station prophylaxis under discipline and uniform application has encouraged an incautious optimism as to its universal applicability to the control problem of venereal disease. Preexposure prophylaxis provides a choice between the condom or sheath and the prophylactic packet. Preexposure prophylaxis without control of the alcohol factor is hardly worth the paper on which it is described.

The condom specifically may be available and be found still in the pocket after the get-together Many condoms prior to the intervention of the Food and Drugs Administration of the Department of Agriculture, which set standards of manufacture and testing, were imperfect. The condom, no matter how perfect or effective, will be rejected after its first employment unless an adequate technic is taught, because it spoils the act "like washing your feet with your socks on. Instruction in the use of the condom by films and others is almost invariably fails to mention that lubrication should be on the inside as well as the outside. At best the condom is, of course, only partial protection in the act itself, and provides no protection in sex play or to uncovered areas. Nevertheless, especially if women could be induced to insist upon its use, it could and very possibly does provide one of the chief barriers against the present day acquisition of venereal disease. Lubricating oils and jellies to be introduced before exposure, and, of course, cervical caps and similar protective devices for the women, are as yet unsatisfactory unstudied, and in their present form, unusable in the casualness and opportuneness of much sexual exposure today The ideal preexposure prophylactic is not a messy ointment or an awkward and repellent mechanical device, but a penetrating, inconspicuous and even colorless substance, which when applied will fix itself in skin or mucous membrane for a considerable period, and may therefore be applied when intelligence can dominate the situation

Post-exposure prophylaxis is stymied by the elements of time inconvenience and discomfort. If and when it is universally enforceable after actual or

assumed exposure as in troops or ships crews returning from leave in a notoriously infected area, they can be subjected to station prophylaxis with astonishing results.

A classical example is Walker's experience at St. Nazaire in World War I, when an incidence rate of 625 per thousand per month was reduced in three months to 110 per thousand by the compulsory application of prophylaxis to all men returning from leave, whether admitting exposure or not. Further application of prophylaxis, and more efficient guards around the camp, reduced the incidence to 35 per thousand. Estimates of the efficiency of station prophylaxis based largely on World War I experience, include such figures as 1.3 per cent failure in 244,000 treatments one infection in 37 exposures without prophylaxis as against one infection in 274 exposures when prophylaxis was taken.

The standard recommendation in all instructional films and lectures for the armed forces in the present war places the optimum time of use as from one to two hours after exposure or sooner if possible the critical question of how large a proportion of exposures is likely to be followed by prophylactic treatment, even if facilities are provided is met by various informal estimates of 1:3 1:5 and even 1:9 prophylaxis taken to exposures made. Washing facilities which recent work indicates are less important than their conspicuous place in instruction suggests, are of all things, most difficult of access under the prevailing casual circumstances of exposure.

It would appear then that the essential conditions of effective mechanical and chemical pre- and post-exposure prophylaxis, are difficult to satisfy They include a measure of intelligence in their application too easily destroyed by the customary or common use of alcohol discomfort and inconveniences discouraging their use even under favorable circumstances nonparticipation and lack of control of the situation by the woman inevitable, almost physiologic delay in the time element of application and evasion of the obligation to take prophylaxis for a variety of reasons if the compulsory or disciplinary use of the method be not employed

An official procedure reduced to formula has been provided as preliminary statement by the special joint committee appointed by the American Social Hygiene Association and the United States Public Health Service published in Venereal Disease Information, 21:311, October 1940 and is quoted as follows: (1) Safest method ( ) use a condom of standard type; (b) thoroughly wash the genitals and adjacent parts with soap and water as soon as possible (the sooner the better but within one hour at most) after removal of the condom. (2) In the absence of condom, ( ) thoroughly wash with soap and water as already described, (b) after urination, inject 6 cc of 2 per cent strong protein silver solution or other efficient nonirritating germicidal solution into the urethra and hold for five minutes, (c) rub 33 per cent ointment of mild mercurous chloride (calomel ointment) into the genitals and adjacent parts. A two-tube formula officially recognized by the Surgeon General's Office United States Army includes 4 grams silver picrate jelly 0.25 per cent strength and calomel ointment 6 grams (this is the official 33 per cent) in separate different colored tubes with appropriate directions, together with a soap cloth and protector for the clothing

The great importance of chemical prophylaxis to the armed forces has led to the recent institution of a number of important studies whose nature and results cannot be disclosed. It is to be expected, however that such studies must include the investigation of penetrant, the incorporation of sulfonamides, the testing of other mercurials than calomel, though it still to date remains supreme and the significance of such ritual procedures as washing with soap and water, the time factor and the local employment of spirillicides of other than heavy metal types. The physician must of necessity therefore, turn to the literature when it becomes available for the recent advances in this field A combined formula of experimental type already published is that of Taylor (U S. Naval Medical Bulletin, September 1943) as follows mercury oxycyanide 0.1 gram sulfathiazole 5 grams, starch (corn) 5 grams, distilled water to 100 grams. For this formula the author claims 100 per cent protection in group of 187 exposed cases, while calomel protargol standard prophylaxis administered to 287 exposed persons failed to protect in seven.

Systemic prophylaxis for syphilis has made no advance and has in fact, retrogressed since the last edition of this work. The history of the procedure including the bismuth plug and the use of stovarsol is given in the second edition. The use of the arsphenamines has succumbed to the uncertainties involved and its further employment is discountenanced. Those who for any reason wish to insist on post-exposure treatment in anticipation of the risk of infection, should carry through the full therapeutic procedure for an established diagnosis of early syphilis.

It is in view of these statements of particular interest that Mahoney and Bryant satisfied themselves that an important, and perhaps the major element in the efficiency of calomel prophylaxis, is the systemic effect of the small amount of mercury absorbed in the procedure. Subsequent studies have tended to show that calomel prophylaxis at least does have an important systemic phase.

Systemic prophylaxis as applied to the control of gonorrhea by the oral use of the sulfonamides, pre- and post-exposure is not here discussed, since it is not within the field of this text.

Prophylaxis and the Professional Infection of the Physician.—On this point so many questions are asked and one is so frequently the recipient of requests for telegraphic and other emergency advice, that two summaries contained in Figs. 213 "To Avoid Professional Infection with Syphilis," and 214 "In Case of Suspected Accidental Infection with Syphilis in Medical Practice," would seem to have practical usefulness. In the majority of cases it is the finding of a positive serologic test in a patient after an accident which inspires alarm. The status of the serologic test here as in all other aspects of the infectiousness of the disease, is, of course beside the point, although the presence of a positive serologic reaction of course directs attention to the risk. A syphilologist who has had any considerable experience with the reaction of his brother physicians towards syphilis in themselves, cannot but regret that a more preventive attitude on this subject and better teaching in regard even to the relatively unsatisfactory procedures available do not prevail.

OCCUPATIONAL AND INDUSTRIAL SYPHILIS

Occupation and industry marshal human beings into aggregates more effectively perhaps than any other agencies except the armed forces. For this reason there has been an almost traditional pressure to induce industry especially to interest itself in the problem of syphilis, not only because of its significance as an industrial hazard, but because of its power as an educative influence in behalf of public health. In time of war occupational shifts, induced by the mobilization of industry have tremendous spreading power as far as venereal disease is concerned, and man-power losses and economic costs due to disability mount in a spiral that compels attention. Industrial losses, destruction traceable to incompetence from diseases, have qualities of sabotage, and this aspect of the matter receives poster recognition in times of total mobilization.

The interest of industry in problems of personnel syphilis has been a slowly progressive and not too easy task. The autonomy of industrial medical groups, their problem in developing their bailiwick to its full possibilities in the face of hard-headed examination of their every claim by management, has probably led to some hesitancy in taking on an additional mass responsibility for what seems to be a matter of general health not to say morals, rather than one of industrial accident and injury. The movement however championed by persuasive and realistic personalities such as Surgeon General Parran of the United States Public Health Service, and Russell, whose special contributions are well known, has in this country had a most beneficial effect.

Industry in fact, in many areas, is "rarin to go" but the supportive public health mechanism still occasionally lags.

That some of the "rarin" is in management rather than in industrial medicine as such, must occasionally be conceded, for the problem undoubtedly seems simpler the greater the distance of the moving agent from the medical problem as such. The lag in public health cooperation is to a large extent result of the elaborate preparation that must be made for an effective industrial policy From the start a mass case-uncovering mechanism in the form of reliable serologic tests in such vast numbers as really stagger the laboratory imagination, is inescapable. For the Philadelphia area for example, it is reasonable estimate that for preemployment tests alone, facilities for 500,000 tests would be necessary within the first year load which the existing public facilities could not possibly undertake to carry without very large expansion and subsidy On similar scale throughout the country the load thrown on the laboratory network could not be met within several years, if not a decade of planning and building. This situation, of course, has been met by certain large industrial groups (*i.e.*, the du Pont de Nemours Company) by the development of adequate intramural laboratory facilities. The relatively small employer is more of a problem than the large one, and the disposition of all employers to "let George (*i.e.* the health authority) do it has been made clear by at least one survey (Pennsylvania Bureau of Industrial Hygiene) The approaches thus far successful have been largely through manufacturers associations and through management and personnel. It remains to be seen how much if any more can be accomplished by laying the baby directly on the knees of its putative guardian—the industrial medical organization as such.

The Prevalence of Syphilis in Industry —Parran and Vonderlehr have graphically presented the situation in a table quoted in Fig. 886. This is the serologic survey approach. A fair picture of the serologic plus the clinical approach is represented by an older study—that of Stokes and Brehmer published as a discussion of syphilis in railroad men.

The industries included in the Parran-Vonderlehr summary may be rated as "heavy Some additional interesting figures include the Endicott-Johnson shoe manufacturing interests, which in 1928 reported 3.7 per cent syphilis in 4117 workers the Seattle City Health Department, 1927 1931 reporting among milk-handlers and drivers of public conveyances 3.7 per cent syphilis among 29,408 persons barbers in Oklahoma in 1938 rated t 13 per cent syphilis; unemployed casual laborers, Minnesota 1931 8.4 per cent syphilis; Eastman Kodak figures, 1.1 per cent syphilis (quoted by Parran, "Shadow on the Land, 1937). Nine railroads requiring tests on routine application for jobs, gave among 21 026 applicants, 7.8 per cent syphilis (Parran, as above) The U.S. Coast Guard (Robertson, 1937) showed an interesting differentiation between personnel in the sea service and the life-saving service 8 7 in the former and 0 4 per cent in the latter For agricultural and industrial labor in the south the estimates run higher (12 to 25 per cent, according to the U.S. Public Health Service surveys) (Lewis, 1937).

The Costs of Syphilis to Industry and Labor —Figures of this sort have still a somewhat speculative character Many of them are old and possibly outdated based on industrial surveys in industries whose identities are concealed and whose representative character for the problem in general over the country at large cannot be determined

Among the most quoted estimates are those of Parker (1934) including 18 per cent syphilis in a group of railway employees, exhibiting delayed convalescence and disability whose total loss of time represented 13,940 day and $48,711 A large industrial concern, unnamed, how personnel efficiency had dropped below expectations, found that one in ten employees had gonorrhea or syphilis 60 per cent of the noneffective employees were on the sick list because of these diseases, and those venereally diseased had lost three times as much time as persons not affected. Each person with syphilis or gonorrhea was paying out an verage of $75 year for such treatment as was being given.

In an ttempt to present the picture graphically Fig 888 was developed as part of the material laid before a conference on industrial syphilis called for the Philadelphia area in 1911 The figures are self-explanatory and are of course, based on the older or standard treatment systems

Fig 896.

SUMMARY OF RECENT INDUSTRIAL SEROLOGICAL SURVEYS*

Location	Period	Number Tested	Number Positive	Per cent Positive
Chicago, Illinois (Average of 350 plants year)	1939	44,015	2,198	5 0
	1940	78,639	1,839	2 4
West Virginia (New River Coal Company)	1931	3,325	302	9 1
	1931 38	8,478	636	7 5
	1938	3,270	220	6 7
du Pont de Nemours & Co. (18 plants, 10 states)	1934–35	27,154	1,063	3 9
	1937 38	50,519	2,030	4 0
	1940–41	35,974	363	1 0
Cincinnati.	1939–40	29,518	1,301	4 4
New Jersey	1939	15,910	267	1 7
Buffalo, New York.	1935–40	4,450	177	4 0
Peoria, Illinois (Caterpillar Company)	1937–40	20,000	160	0 8
Alabama (Alabama Fuel and Iron Company)	1937 39	3,146	333	10 6
Indiana Harbor (Inland Steel Company)	1937 39	10,000	488	4 8
Oakland County Michigan	1938	11 737	603	5 1
Ingham County Michigan	1938	1,547	24	1 6
New York City (Metropolitan Lif Insurance, Home Office)	1939	12,141		0 5 (Approx.)
Montana (No. Pacific Railway Company)	1936–38	2,656	64	2 4
Schenectady (General Electric Company)	1940–41	13,963	102	0 7
Milw ukee, Wisconsin.	1939–41	32,902	520	1 6

Reprinted by permission from "Plain Words about Venereal Disease by Thomas Parran, M.D and R. A. Vonderlehr M.D Reynal and Hitchcock, Inc., New York City 1941 Those interested and wishing to read further on this subject, see the volume above referred to, and Dr Parran earlier book, also published by Reynal and Hitchcock, "Shadow on the Land.

Fig 897

SYPHILIS IN VARIOUS OCCUPATIONAL TYPES (Stokes and Brehmer)

Occupational Types	Men Only		Husbands and Wives	
	Cases	Per cent Syphilis	Cases	Per cent Syphilis
Railroad employees	128	11 7	184	10 3
Laborers.	243	6 1	297	8 8
Business men (tradesmen, merchants)	236	3 8	311	3 2
Farmers	536	1 3	863	1 4

The low percentage of farmers with syphilis accords ith Parran reports of the U ited States Public Health Service figures and the synopsis of the final report of the British Royal (Sydenham) Commission, which indicates that agricultural laborers are relatively free from the disease. Of 1145 men examined i the M yo Clinic survey 4.2 per cent had syphilis; and of 514 women, 2 6 per cent had syphilis. The relatively low proportion of syphilis in these figures is probably affected by the source of the clientele of the M yo Clinic, which is drawn from the population of the section of the United States in which the survey of the second million drafted men in World War I showed the incidence of venereal disease to be very low

which can undoubtedly be materially reduced by the adoption of duty-status technics as they develop. The cost figure for syphilis at estimate of $8 per 10-hour day which is obviously low for many important categories on a war wage-scale, amounts to $7 440,000.

The cost of syphilis in the key person is emphasized by the last caption of Fig. 888 "and it depends on the man." This point is repeatedly and justifiedly emphasized in propaganda, and the enormous—indeed the immeasurable—cost to business in the "nervous breakdown" initiating paresis in important executives and business heads can be substantiated by example. More graphic for the commonalty however are some of the examples from the publication of Stokes and Brehmer on syphilis in railroad men, and Stokes and Ingraham in "Syphilis and the La

A yard-master whose last routine medical examination preceded his symptoms by approximately five years, but who had been under the care of railroad physicians for fourteen months, came to the Mayo Clinic for supposed laryngeal tuberculosis. He had never had a Wassermann test according to his statement. On the finding of a positive test, he was placed on treatment and made a remarkably rapid and satisfactory recovery. His history showed that he had developed a mass on his shoulder probably gummatous, following injury in line of duty through which he was endeavoring to collect compensation from the road. He had at a previous time received compensation for complications following another injury which suggested the influence of syphilis

Fig. 888.

MAN-HOUR COSTS OF VENEREAL DISEASE

Disregarding loss of efficiency slowdown and critical mistakes from illness with, or the effects of treatment for venereal disease, the hours potentially lost per infected and treated man may be estimated conservatively as:

Syphilis	500 man-hours in 65 weeks
Gonorrhea	*80 man-hours in 10 days*

Using the rate of 30 per thousand for syphilis in industrial workers recently established by surveys covering 267 000 employees in a national industrial personnel of 10,000,000 men:

Syphilis Can Cost.	93,000 000 man-hours spread over at least 65 weeks
Gonorrhea Can Cost.	7 000 000 man-hours spread over 8 weeks

100,000,000 man-hours

A 100-Hour Battle by One Million Men, LOST

And syphilis alone keeps on costing at a minimum of 15,000,000 man-hours a year—

AND IT DEPENDS ON THE MAN

A screwy pilot (with syphilis of the brain, or taking "tablets" for gonorrhea) can crash 400,000 man-hours of bomber in one motion.

as a cause. In addition to the foregoing he had been a continuous source of expense to the railroad for fourteen months during the treatment of a nonexistent tuberculosis, only to have the real nature of the trouble identified by a Wassermann test. A locomotive engineer age thirty-six at the time of his physical examination in the Mayo Clinic complained of difficulty of urination, for which a physician had been treating him with sounds, on the supposition that he had a stricture. On examination he was found to have a positive Wassermann, neurologic findings fairly distinctive of taboparesis. This patient was under observation and intensive treatment for one and a half years, in the premalarial era entered a definite remission, and during a period of about six months successfully carried his usual run. Suddenly however he returned to the clinic for observation, and it developed that he had been given "90 days" for his responsibility in a passenger wreck. As the patient expressed it one of his "spells" (lapses of memory) had come on him while on the engine and he had passed a siding where his orders were to meet another train. An examination of his spinal fluid at that time showed a rapidly advancing process in his central nervous system apparently unaffected by the treatment he had received. We could find no evidence that the railroad employing the man had made any effort to identify a possible medical factor in his responsibility for the wreck. Still another locomotive engineer in charge of a large superheater was suddenly seized with an irresistible impulse to ram the trai he was about to haul to the yards. He forced himself to close the throttle set the emergency air turned the engine over to a fire-

man, and following treatment for his neurosyphilis subsequently discovered, recovered sufficiently to go back to work. Still another yardmaster hit on the back by a brake-club, was catheterized for two weeks in a railroad hospital without a definite diagnosis. He was proved ultimately to have neurosyphilis, responsive to treatment.

The Definition of an Industrial Policy—Industrial policy must take on the color of the individual situation without doubt, as in most venereal disease control problems. There is, however, a fabric of underlying principles, which, from our experience and the literature, we have endeavored to summarize in Fig. 889. The first three captions, referring to the serologic test, are self explanatory, but Item 5 properly emphasizes that there is existing case material to justify—namely, the obligation of an industry which establishes its own laboratory or uses any laboratory facility, to see that such a facility measures up to all the national and state standards of approval now in exist-

Fig. 889

SOME INDUSTRIAL SYPHILIS PRINCIPLES

1. Serologic tests in preemployment examination and periodic reexamination are not the whole answer.
2. Serologic tests on candidates for employment should be routine and routinely a part of physical examination.
3. The serologic test should conform to all accepted standards as to laboratory fitness and procedure.
4. The possibility of false positives should be considered and checked.
5. Identified syphilis should not be dealt with simply on a blood test, but classified by fuller study—i. e., early, latent, CNS, cardiovascular, special sense organ.
6. For the community the first two, for the job, the last three are the most important.
7. Syphilis does not, as such, disqualify for a job (even as a food handler) nor does it justify a fire-on-sight policy.
8. The industry has a powerful leverage, in the job, for holding the employee to treatment which can insure fitness.
9. Such treatment, either given or positively arranged for, is an industry's duty.
10. Cooperation with organized labor is desirable and of great assistance in securing 8, if 7 is adhered to.
11. The industrial medical staff should utilize the services of the public health authority, report cases to them and make use of this assistance in contact-tracing and in the control of recalcitrants.
12. A very moderate expenditure of effort yields large returns in (a) increased safety, (b) less compensation costs, (c) increased employee confidence and cooperation, and (d) reduction in syphilis.

ence. The harvest of false positives and false interpretations where this is neglected can be large and serious. Industrial physicians, responsible for the interpretation of test results, should be familiar with the necessary checks on positive tests (which should always be repeated) and should be familiar with the causes of biologic false positives as now understood. They may require expert assistance and interpretation, which *should* be available *through* the public health authority.

Great stress should be laid on the classification or work-up of all syphilis identified in an industrial group.

Moore (1937), in his editorial expressions on this problem has particularly emphasized this point, and Cochrane and Kemp (1937) have shown that industrial disability and possible compensable injury may actually develop on the job from cardiovascular syphilis in unrecognized victims of the disease. For the public health, syphilis should be classified into early (infectious),

late symptomatic and asymptomatic types. It is the symptomatic syphilis, of course, which is critically important, but it should be pointed out that asymptomatic neurosyphilis, especially should be identified by spinal fluid examination whenever the individual case seems to justify it. This, for example, is the practice of the Baltimore and Ohio Railroad, as reported by Mulholland, and is particularly necessary in this type of industrial work.

All policy formats for industry to date begin with the positive assertion of Item 7 even more vigorously and uncompromisingly phrased. Reference has already been had to the fundamentally unsatisfactory character of job or occupational syphilis-finding activities, because serologic tests do not define either infectiousness or competence with respect to the particular work in hand, or in prospect. That there is such a thing as job fitness with respect to the presence of syphilis, however, should not be minimized or denied, and whereas an individual may be permitted one type of work in the face of one type of syphilis, he should be denied it if the type of syphilis either involves risk of inadequate performance, risk of extension under strain; risk for fellow-employees, or risk to the public health.

All proponents of industrial cooperation in syphilis control appreciate the tremendous leverage exercised by industry in behalf of adequate treatment and feel that industry should recognize its power by a corresponding sense of duty and should arrange for, supervise and assist in holding to treatment all individuals for whom it accepts any responsibility at all. Some of the difficulties that industry may encounter in trying to carry out this duty are vividly described by Gehrmann of the du Pont organization, and justify the suggestion that if private care is inadequate, the public health authority, through its clinics, should be drawn into the picture.

Many of the initial difficulties in the industrial field arose from an antagonistic attitude on the part of labor, which felt that blood testing was a discriminatory device containing an element of unfairness to the employee. That this reaction can be largely disposed of by a full statement of the situation and frequent conference with organized labor has now been clearly demonstrated. In fact, the influence of organized labor is a potent means of controlling the floater and the recalcitrant.

Sayers (1939), of the Division of Industrial Hygiene of the National Institute of Health, lays an excellent foundation of principles, some of them already alluded to with reference to the significance of syphilis for various types of occupation. He points out that while broad administrative policies may be defined, the decision as to what shall be done about syphilis of the employee in industry must be based upon a consideration of the individual case. In doing this, two groups of variables appear: (1) the particular job, its requirements and responsibilities, and (2) the particular syphilitic, the stage of the disease and the treatment taken. When one considers the job, there seem to be four principal sorts of human relationships involved, three of which concern industry. The other, or the individual job, is more or less distinguished by the fact that it is not integrated into a larger enterprise, such as the job of the farmer, the artist, or the prospector for example. Sayers divides jobs as follows: the personal contact job, in which it is important to keep alert for early syphilis. Among these he classes food handlers, hotel workers, barbers, beauty parlor workers, pullman porters, matrons, nurses and school teachers. He might well include all classes of domestics. His second classification is the job of responsibility: air-pilots, engineers, operators of switches, train dispatchers, crane operators, financial executives, for example. Among these, late syphilis as recognized by special tests and special examining acumen is highly significant. The third classification is that of the routine jobs such as clerical workers, laborers and so forth, in which he rates syphilis as of less importance but still a factor.

With reference to infectiousness, Sayers' emphasis deserves amplification. It is a concern of the employer, for example, that the waitress in the company restaurant, who is acting as the disseminator by clandestine prostitute activity with employees, shall be rated as an industrial hazard, precisely as is the employee who handles the lettuce or passes the towel from one person to another. D. C. Smith (1930) has emphasized the practical importance of the intramural carrier in a large group centering about a small industrial plant employing young men and women. The plant was thirty miles from the clinic. Fifty-seven names of exposed persons were obtained by messages of patients and correspondence. Twenty-four persons were examined in the clinic and gave negative reactions, and fifteen were found to have acquired syphilis. In fact, it is quite conceivable that the syphilis transmitted through the intramural sexual contacts of syphilis-infected employees is a more important issue than the transmission of syphilis through the medium of food, articles of common use and the like.

In all consideration of industrial syphilis, trauma looms large and the discussion of the topic in Chapter I should be referred to. Klauder and Solomon (1931), and Klauder individually point out that industrial compensation laws now abolish the defense of contributory negligence. Hence, it is no defense for the employer to show that preexisting disease brought about accident. In fact, Klauder's (1933) contribution on interstitial keratitis and trauma should be read by

every industrial physician, and its principles become familiar to industrial executives and medicolegal counsels. Eliet, under the professorship of Jeanselme laid down in 1936 a summary which is constantly quoted by persons concerned today with the influence of trauma in syphilis (Besson 1936). His classification of its effect includes (1) single and violent trauma; (2) single mild trauma; (3) mild trauma repeatedly applied. For all of these the industrial physician should be constantly on his guard in evaluating the potential significance of syphilis in an employee for his company. The activation of neurosyphilis, particularly by trauma (Urechia 1936, Barthelemy 1930) is often startling and serious. The question of infectiousness is an angle of the trauma issue, for *Spirochaeta pallida* may appear in early syphilis in lesions induced by vesicants and other traumatizing agents (Frankl 1936, May 1931).

Serologic Misinterpretation and the Job.—The foregoing discussion has related largely to the use of serologic tests, and some reference must be made to its abuse, especially where the law intervenes in a compulsory role. These misinterpretations are the not unjustifiable basis of labor opposition to extensive applications of blood testing in industry. A typical case, illustrative of the arbitration of individual issues, medical merits and personal rights by an incompetent arbitrator and the misuse of a positive serologic reaction as a pretext for a discharge actually based on other and personal ground, is illustrated by the following case.

A kitchen worker attached to the staff of college training table, who without preliminary medical examination had been employed by the college for six months and proved to be thoroughly efficient, was then subjected to routine serologic and physical examination; the blood reaction was found to be positive by the State laboratory. As was proper under the circumstances, he was referred to the College medical clinic, having charge of syphilis, and was found to have a seropositive latent infection of probably not less than twenty-six years' duration, the patient being at this time forty-six years of age. Before it was possible to work up the case or have competent medical opinion on his status, the nurse attached to the training-house squad discovered in some way that the patient had been referred to syphilis clinic for study, and without further information on the matter took the information to the lay superintendent of employees in this group. The lay superintendent and nurse, again without referring the matter to the physician who had originally recognized the presence of syphilis in the employee, proceeded directly to the syphilis clinic in an effort to obtain information as to whether this employee had syphilis. Information was properly refused them on the ground that they were laymen, and that the patient was privileged in the matter of communication. Thereupon these two lay persons, considering further reference of the matter to medical authority unnecessary, took it on themselves to discharge the employee on the ground that he had syphilis and that his association with food-handling work on the training table made him public health menace. Thereupon the clinic in which the man's infection was under study went back to the physician in charge of the case with its report, and by conference with him, and with the cook in the kitchen, succeeded in securing the employee reinstatement, since the syphilitic infection was absolutely without significance for the transmission of the disease.

The Reduction of Syphilis by Industrial Action.—A valuable table (Fig 890) from data in Parran and Vonderlehr "Plain Words about Venereal Disease" (Reynal and Hitchcock, 1941) shows graphically why the public health authority and the syphilologist desire the aid of industry in the control of infection, and why industry is justified in rendering such aid.

One of the industrial concerns mentioned previously as having noted conspicuous lack in personal efficiency which, on investigation, was ascribed to the prevalence of venereal disease, established clinic within the industry for adequate treatment, and discovered that it promptly offset the cost of the establishment by increased production. A West Virginia manufacturing concern, as result of the installation of clinic for venereal disease, costing $5000 to $6000 for the first year sustained an increased efficiency of 25 per cent. Undeniably the cost-accounting and personnel divisions of large industrial concerns could make stimulating and important contribution by closer study of this question.

Fig. 880

THE REDUCTION OF SYPHILIS IN INDUSTRY IS POSSIBLE WITHIN A PERIOD OF A FEW YEARS*

(1931 1934)

	Size (Number Employees)	Years	Prevalence of Syphilis in Employees
New River Coal Company West Virginia	3,300	1931	9 1%
		1931 36	7 2%
		1936	6 7%
du Pont de Nemours Company (18 plants, 10 states)	40,000	1931–33	8 9%
		1937–38	4 1%
		1940–41	1 9%
Caterpillar Tractor Company Peoria, Illinois	20,000	1937	4 6%
		1941	0 8%
General Electric Company Schenectady New York	14,000	1932	4 4%
		1939	1 8%
		1941	0 7%

From Parran and Vonderlehr R. A., Plain Words About Venereal Disease, Reynal and Hitchcock, Inc., New York City 1941 p 212.

ORGANIZATION FOR AN EMERGENCY VENEREAL DISEASE CONTROL SITUATION—CIVILIAN PROGRAM

A preliminary bow of credit should be given in such a discussion to the importance in time of emergency of the preemergency forces and set-ups which have been concerning themselves with the entire front of venereal disease control (Blue-print Fig 876) In direct proportion as a community or a nation has concerned itself with the problem before it becomes acute the result of emergency effort will be distinguished or mediocre From the civilian standpoint, at the present day much of the organizational effort expended on venereal disease control has followed the "association and education technic" as it might be called. In other words, it has undertaken to gather interested persons into chartered groups, serving as centers of influence and distributors for what is essentially propaganda or educational material. More infrequently such associational activity has concerned itself with the building up of intramural cooperation among the various groups or elements in the agency category confronting the sectors in Fig 876 When an emergency develops, the pressure for getting something done quickly results in a distinct shift towards what might apologetically be called the Fascist phase of a democratic procedure This means a resort to the key persons of high initial energy and acquaintance with the field who are given mandates under Defense Council authority either to head or to organize small committees which thereupon proceed to a further search for and enlistment of key persons, and the repeated and systematic employment of conference in an effort to galvanize and knit together the activities of the more central members of the agency front. The key to the key-person technic is of course influence and acquaintance as well as knowledge of the field As the civilian committee unit expands its activities, it undertakes to inform the public of the course it is pursuing but it relies on the public only secondarily and wastes as little time as possible in torchlight

processions and propagandistic publicity The earlier contacts made by the civilian VD defence group with the health authority the courts, the police, the prosecuting attorney and the liquor control agencies, are its contribution towards what might be called "the gang-up approach" to concerted effective action. This gang-up should, of course, follow a rather careful consideration of the precise nature of the local field, and a decision as to the points on which greatest pressure must be exerted to produce maximum control effects. The maintenance of adequate continued pressure is, of course, the chief problem for all public movements in or out of emergency situations have the initial emphasis of the rocket and a tendency to final flop

The selection of important social and industrial units through which to exert pressure or initiate movements is often determined by the finding in such units of key individuals who are both interested and active or willing to become so. Thus traction authority may be induced to publicize on tremendous scale, as in the car advertisement shown in Fig. 885 which through key person approach was placed in all the vehicles of the Philadelphia Transportation Company Industries may be induced to lend few minutes of industrial time to forceful moving picture; department stores may participate in employee and public education. The County Medical Society must be approached in manner to enlist its support and give it due place and importance; *broadly speaking no single agency has so much power to bog down movement so dependent* on the fundamental public health principle of treatment of the infected individual as does the medical profession. *Pari passu*, no single influence, probably has greater power to activate public sentiment when once it is willing to take the field. The technic of the original organizing and stimulative VD defense group should include the invitation t membership of representatives of the gang-up agencies. It should scrupulously preserve both the open forum and freedom of discussion technic, within its own membership, and absolute privacy and respect for off-the-record communications The importance of military and naval uniforms cannot be over looked in war emergencies and their presence often makes the difference between action and desuetude.

Thus, comparatively small group can provide the yeast for considerable rising of substantial bread in the emergency control of venereal disease. Such groups usually find to their astonishment that they are by no means alone in their efforts and desires, and that the front is closely defended, not to say at times obstructed and bestrewn by other groups intent on similar laudable purposes. After such statement the mention of any specific groups might be considered invidious; but unquestionably local sentiment not being too jealously isolationist, the state and national resources indicated in the blueprint should be invited to participation early in the work. In fact, it has been said that nothing gets to nowhere in the local infection control problem until the FBI takes *over the scrutiny of bank accounts and income tax returns. This points the moral* for the prosecuting attorney and for all others, that finding the vested interests, isolating or reforming or punishing the facilitator is one of the chief works of long range civilian cooperation and program control.

The disposition in old line thinking to leave venereal disease control to the police and the courts is sometimes an explanation of a halting and jerky raid-punctuated program Common sources of difficulty are of course familiar enough to the slightly cynical reader The police throw out the dragnet, gather in the known prostitutes, and then are chagrined to find them discharged though undoubtedly guilty of violation of the criminal code on the basis of a negative medical examination. The prosecuting attorney finds it difficult to prepare cases in the absence of witnesses, many of whom wear uniforms. Politics dominates many of the smaller centers of legal decision, and interest pulls every leg that it can find. The liquor control authority as has been many times indicated, holds one of the critical strategic positions without, unfortunately in many cases, a sufficiently extended power to enforce. The health authority too often is looked upon by the old-line workers in the field as an interloper respectfully addressed as "doctor" but regarded as one who

should stick to his statistics and let the vice squad and the wagon do their work unhampered. The disposition to adopt stop-gaps and chase dogmatized solutions particularly such as the wholesale incarceration of prostitutes, appears and reappears, and the press, too often enlisted with great difficulty in a sober and well-thought-out presentation of any problem will quickly make a sensational issue of a nonessential Broadly speaking, in the present emergency press cooperation has been so far as we have observed, more difficult to obtain than that of any other publicising agent.

VENEREAL DISEASE IN THE ARMED FORCES

Army and Navy Rates.—The student of venereal disease control owes a lasting debt to Colonel J F Siler whose monumental analytical study of venereal disease in the Army of the United States of America throughout its history is literally a textbook unsurpassed in the world literature From this source from the statistics of diseases and injuries for the calendar year 1939 in the Annual Report of the Surgeon General of the United States Navy (with comments) published in 1941 and from a statement read by Commander Carter before the Special Committee on Enforcement of the National Advisory

Fig 801

VENEREAL DISEASE ATTACK RATE PER 1000 PER ANNUM FOR THE ARMED SERVICES IN THE YEARS IMMEDIATELY PRECEDING AND DURING THE FIRST 18 MONTHS OF WORLD WAR II

Year	Army	Navy
1939	30	66
1940	42 5	59
1941	41 5	51
1942	38	56
1943 to August 31	25	—

Police Committee on Social Protection (Journal American Medical Association, 122:311 May 29 1943) we have collected the figures to place the venereal disease incidence problem of the armed forces in their American perspective (see Fig 801) From Colonel Siler s monograph, Figs. 802 and 803 are reproduced the former because it shows, together with incidence in the Army as a whole the striking effect of foreign service on venereal disease incidence controlled and uncontrolled, and the latter because it correlates the ups and downs of incidence in an armed force with important events and regulations in the control situation. From these figures and summaries it will be apparent that the United States Army has been able to introduce into human experience as determined by wars, the paradox of a drop in venereal disease incidence of the most striking proportions in complete violation of the experience of history our own included that venereal disease rates in armies and navies should rise enormously during wars. The Navy has in World War II accomplished a similar feat (Fig. 801) In the case of the Army it may perhaps be broadly said that this triumph is an expression of the weight of a determined central policy enforced at the periphery against what might be called the minor antagonism of the old-line opposition which has supported regulation as against suppression In the Navy as no doubt in the Army a large part of

Fig 892.—Venereal disease, United States Army since 1820, annual rates per 1,000 strength. (The Army Medical Bulletin No. 67)

(American troops only)

Note: American troops in China where not shown are included in Philippine Island figures.

Fig 893.—Admissions for venereal disease, annual rates per 1,000 strength, United States Army by country 1900–1940. (The Army Medical Bulletin No. 67.)

the improvement must be attributed to attention to preventive detail at the periphery In the Navy the autonomy of the ship and the fleet operating often in the worst imaginable conditions as regards milieu in the tropics and the Asiatic countries, the importance of the ship's medical officer the fleet medical officer and the rapport between them and the fleet command, must have special significance and this demonstration that it has reached its full effectiveness is especially welcome.

Several points deserve comment on principle. First, the rates presented are *incidence* or attack rates and there is nothing comparable with them in experience with respect to the civilian population. They are based, and the possibility of obtaining them depends, on the medical physical inspection possible only under the disciplinary control of the armed forces. In civil life a large part of the incidence of venereal disease disappears into the limbo of nonexamination. The second point concerns the use by the Army in the more recent statistics, of so-called *adjusted rate* which excludes those cases which appeared with venereal disease at their first assignment to camp, presumably acquired en route after examination at the induction center This, of course, results in a striking drop in incidence figures, but it raises the uncomfortable and probably as yet unanswerable question as to whether the armed forces have any responsibility for the condition in which their inductees arrive and if so, what forms of pressure they can bring to bear to protect them during the immediate preinduction period. That such responsibility could not with justice be placed solely upon the armed forces is clear but the desirability of their initiating an energetic movement for the correction of the discrepancies is, we believe, equally clear The third matter for comment is the special conditions encountered by the *Navy* Throughout its history the Navy has had a higher incidence of venereal disease in times of peace than in time of war because in war the personnel is distributed to ships and fleets which are on the move and for long periods of time out of access to venereal infective sources. That such condition of affairs need not necessarily prevail, and that tropical service or not, the Navy should be controlling the situation in time of peace with something approaching the circumstantial efficiency of war would seem to be at least a permissible deduction. Nonetheless, the greater difficulty of organizing the small unit groupings of the Navy must be admitted. In armed forces whether of the land or the sea, there will inevitably be a fraction of the medical and line personnel unacquainted with advances in venereal disease control practice, and if acquainted, disposed to differ because of limited personal observation of some limited local solution of problems which has little or no general application. The Navy in the present war has laid great stress on the educational responsibility of the individual officer with respect to his men, and has been placing increasing reliance on preexposure, especially mechanical prophylaxis, and on the most systematic advocacy if not enforcement, of early postexposure prophylaxis. The records on some individual ships are almost too good to believe and are convincing demonstration of the effect of locally applied force, energy and foresight in dealing with the infection problem.

The history of Army practice is particularly well displayed in Colonel Siler's diagram (Fig 892) The war peaks are obvious, but more important is the record following the Spanish American war and the Philippines insurrection, in which the influence of voluntary prophylaxis, instruction in sex hygiene, compulsory prophylaxis, monthly physical inspection and forfeiture of pay began to become apparent. The comparatively low figures in World War I high in contrast though they are with those of the present war are also expressions of a determined central policy initiated early in the conflict, and adequately implemented by sections 12 and 13 of the Selective Service Act, which provided control of extracantonment and leave conditions and the alcohol situation, which was slow in developing in the present conflict. Colonel Siler explicitly and repeatedly emphasizes what is coming to be regarded (Pappas 1943) as first principle of venereal disease control official recognition of the responsibility of unit commanders for the rate prevalent among their men. This again points the principle that the control of venereal disease is local and indeed an individual matter eye-to-eye and man to man. There can never be substitute in directive letters, general orders or statements of policy for the energetic and determined as well as enlightened medical and line officer

A Summary of Control Principles for the Armed Forces.—This has been attempted in Fig 893 and inasmuch as a large part of the volume of informational material, as well as the preponderance in man power comes from the Army side it may have a distinctly military flavor Nonetheless the emphasis

is nearly equally distributed. Venereal disease comes from the civil population. That portion of it which distributed venereal disease in former wars remained relatively stationary about points of troop concentrations. In this mobilization it moves with the troops, or the troops on leave move towards

Fig. 804.

SOME CONTROL PRINCIPLES FOR THE ARMED FORCES

1. Venereal disease comes from the civil population—but this does not relieve the military and naval authority from the duty of protection of personnel en route and on duty and an interest in public health.
2. Control problems are fundamentally local, with general phase, not the reverse.
3. Cooperation with the local health authority is vital.
4. Such cooperation requires
   a. Accurate contact tracing and other information freely exchanged;
   b. Centralized (venereal disease control officer) responsibility in major units and concentrations, on both sides (i.e., military or naval, and health authority);
   c. Frequent conference.
5. Suppression of opportunity for exposure to potential infection not mere regulation of prostitution, is the demonstrated, not just the rhetorically sound policy
6. Suppression should be encouraged and left to the civil authority as long as possible.
7. Venereal disease control officers in the armed forces should participate actively in public education and the securing of professional cooperation.
8. Within the armed forces themselves the following policy items are essential
   a. Central directive influence;
   b. Cooperation and sympathy between venereal disease control and general medical and line officers,
   c. Development of adequate personnel to obtain usable epidemiologic information within the corps itself
   d. Adequate planned prophylaxis, pre- (condom and kit), and post-exposure (station)
   e. Adequate forceful and repeated vivid instruction in small groups and man to man, not in occasional casual mass aggregates
   f. No "pro-slips"; contact-tracing based on source of infection (via the infected man);
   g. Study of the leave area and out-of-bounds; military police, shore patrol and Navy Act second or last;
   h. Willingness to have uniformed personnel appear in support of civil effort and court action where indicated
9. A positive attitude of responsibility placed on all concerned for the incidence of venereal disease in command or group—i.e., on the personnel to report infection (not necessarily exposure) and on line and commanding officers to account for their venereal disease rates and accept them as grading factors in promotion, etc. It is recognized that penalty too directly applied encourages concealment and self-treatment.
10. A positive attitude on morale factors. Don't just leave it to the chaplain.
11. Four additional suggestions
    a. That treatment for venereal disease be so far as possible conducted on duty-status basis (Pappas);
    b. That the post be made more attractive than the undesirable leave area ("barrios" of Philippine practice—Siler and sports-recreation principle advocated by Wenger);
    c. That training be conducted when possible in areas with low indigenous venereal disease rates (Wisconsin-Minnesota mobilization) and
    d. That extraordinary precaution and special preparation combining civil and military effort be devoted to venereal disease control in advance of occupancy (Wisconsin mobilization) and in tropical and certain foreign stations.

widely scattered sources with a new and disconcerting fluidity. Army conditions now begin to approach the "sea-gull" situation in the Navy in which the girls move back and forth from station to station with the fleet. This extends over the entire countryside for distances ranging up to a thousand

miles from the point at which an individual infection appeared, the general problem of control and makes doubly necessary the inter-state and inter municipal not to say national public health mechanism for the handling of the situation equally with the closest possible inter-digitation between the military medical organization and the civil public health authorities. The first duty, therefore, of a medical officer charged with responsibility for venereal disease is to accept himself and to sell to all concerned the principle of suppression as opposed to regulation and tolerance. He should not feel himself restricted in his approaches to the civil population, but should at the earliest moment cultivate the closest possible relations with it and particularly with its public health representative Much travel and constant conference and interchange without the stiffness but with the prestige encouraged by the uniform is a necessity In March, 1942 for the first time in its history the Surgeon General's Office of the United States Army announced that specifically qualified medical officers would be assigned to control and prevent the spread of venereal disease among our troops, and the Venereal Disease Division was placed in charge of Colonel Thomas B Turner formerly of the Johns Hopkins School of Public Health and a syphilologist and laboratorian of distinction. From this point onward the force of the jointly announced policy of the War and Navy Departments the Federal Security Agency and the State Health Departments (Venereal Disease Information, September 1940) gradually became a reality The delays heatedly discussed from various sources have not apparently seriously affected the ultimate good results, although the question again of an adjusted rate and nonresponsibility for preinduction infection arises to plague the inquirer Some of the delay was perhaps consequent on a disposition on the whole a wise one, to endeavor to proceed to the control of local situations by building up local support and enforcement in contrast with the use of the big stick and F B.I approach.

The value of planning which includes all agencies civil and military including the public health and police authorities, the beverage control, highway and automobile control, and similar authorities, was effectively illustrated by the pre-war Wisconsin and Minnesota mobilization in which, vested with the necessary constitutional authority the governors of the states concerned as an emergency measure were enabled to call together conferences of the interested authorities to set aside as segregated or controlled area, the entire region of mobilization as special public health district. The individual functioning state services were able to prepare the terrain for occupancy and to frighten off it is believed, wholesale influx of subversive influences. The results in the Wisconsin area: 60,000 regulars and National Guard troops, total of 78 cases of venereal disease admitted to hospital, only four of which could be definitely traced to infection received in the maneuver area, a rate of 0.65 cases per thousand per annum. A critique of these figures must take account of the relatively short duration of the maneuvers, which failed to reveal perhaps all infections acquired during them; the great activity of the troops which through sheer fatigue, limited their capacity for acquiring venereal disease, and the high morale of experienced soldiers and the pick of the National Guard, many of these men in middle life with family and personal responsibilities acting deterrents.

The Military Mechanism—Selective Service Contact Tracing, Power to Act.—The policy of the armed forces of the United States in the present war with reference to the acceptance of men with venereal disease began with an absolute "No, and then as man power pressure increased the gates were cautiously lifted and at the time of going to press the general policy of admitting selected persons with syphilis to the armed forces has had full acceptance An effort has been made to preserve the general principle that a man with venereal disease admitted must either have had or would after

induction be given an amount of treatment which an advisory group (the Venereal Disease Subcommittee of the National Research Council) felt willing to define as adequate treatment for his infection. This admits to service a relatively large body of usable material in the early and latent phases of the disease cripples if it does not outright do away with the malingering device of acquiring a venereal disease in order to avoid induction and subjects a large mass of human material to a better evaluation with respect to blood serology and spinal fluid and clinical examination, than it has ever received before. The exclusion of recognizable cardiovascular and neurosyphilis is absolute and its identification after induction is made the basis for medical discharge. This too may be subject to new directives.

The recognition by the Army of its share of the responsibility for the tracing of the infectious contact is one of the notable advances in the practice of the present war At the start, the Army's share in the identification of the source of infection consisted in making available to the local public health authority the prophylaxis slips made out by personnel visiting prophylactic stations after exposure. The worth of the information was small though in expert hands, by no means negligible. Intoxication, unwillingness to testify fuzziness of recollection, fear of medicolegal complications, all diminished the usefulness of the "pro slip" and it required a high order of expert contact tracer to "stack" these slips in such a way as to bring out the identities of important promiscuous and infection-distributing individuals. There was increasing reason to believe that the necessity for filing a "pro slip" deterred a large proportion of personnel from seeking prophylaxis after exposure, and emphasis on its use has accordingly steadily diminished With this decline has arisen a far more effective approach namely by way of the infected individual after his acquiring of a venereal disease is established at his post. The report of contact of venereal disease reproduced as Fig. 895 illustrates the use the Army has made of the developing knowledge of source of infection. The information is collected from several different types of adjunct personnel within the Army medical organization itself but particularly from corpsmen and noncommissioned officers, whose contact with troops is extremely close. In some instances, public health nurses in the employ of the civil health authority have participated in this work with notable or negligible results dependent on various circumstances. This form of report is addressed to the health officer a sign of the new cooperative relation between the civil and the military authorities

The Third Service Command, with which we have had special experience, and whose results have been effectively published (Norris, Doyle and Inkrant 1943), has illustrated number of important changes taking place in the venereal disease situation of our armed forces, and embodies demonstration of the effectiveness of military-civilian cooperation in control. For the sixteen months period, March 1942, to June 1943, 4,198 cases of venereal disease contacts (both gonorrhea and syphilis) were reported by the Third Service Command to the health departments of the states and cities concerned. Family (ife) contacts represented 9 per cent of the sources of infection casuals (friend, pick-up, no-fee-paid) 73 per cent of the contacts; and prostitutes including streetwalkers, brothel inmates and call-girls, represented only 18 per cent of the infectious contacts. The shift in the present war and American scene from professional to casual source of infection could not be more clearly illustrated. The age group distribution of the contact sources of infection presents disconcerting food for thought. One-third were between fifteen and nineteen years of age; 47 per cent in the early twenties (twenty to twenty-four), thus placing the problem statistically squarely in the lap of youth, and difficultly controllable youth at that. In supplementary report (Venereal Disease Information) of interest to control agencies, is the item of the foregoing report ... hich classifies the changes in the sites of encounter and exposure. The

Fig 895.

Form 149
MEDICAL DEPARTMENT U. S. A.
(Authorized Oct. 20, 1942)

REPORT OF A CONTACT OF VENEREAL DISEASE

STATION

T Health Officer Date

A soldier (Serial number) (Organization) (Race) (Age) infected

with (Name of disease) exposed on (Date) at (Hour) and whose

symptoms began (Date) and diagnosis made on (Date)

gave the following information.

CONTACT HISTORY

ALLEGED CONTACT: Name (and nickname)

Address (Number street, and city)

Race Age Height Weight Color eyes Color hair

Other descriptive features

Occupation Place of employment

TYPE OF CONTACT: ☐Wife. ☐Friend ☐Pickup. ☐Streetw lker ☐Brothel. ☐Call-girl.

PLACE OF EXPOSURE ☐Home. ☐Hotel. ☐Cab. ☐A t or trailer ☐Brothel. ☐Other.

Name and address of place of exposure

CONDITION OF P TIENT T TIME OF EXPOSURE: ☐Intoxicated ☐Drinking moderately ☐Sober

PROPHYLAXIS ☐None. ☐Condom. ☐Self-administered chemical, type.

Official station (Address) D te. Hour

PROCUREMENT HISTORY

PROCURER ☐Own effort. ☐Pimp. ☐Cabman. ☐W iter ☐Bellhop. ☐Newsboy ☐Other

Description of procurer

PLACE OF PROCUREMENT OR ENCOUNTER ☐Bus or R.R. depot. ☐Hotel. ☐Cab. ☐Street. ☐T vern. ☐Dance hall. ☐Poolroom. ☐Private property ☐Other

Name and address of place of procurement

AMOUNT P ID T hom ☐Contact. ☐Procurer ☐Other (specify)

REMARKS

Please report the results of your investigation on the reverse of this form.

(Signed)
(For instructions and distribution see final sheet in this pad)

tavern class, hich includes restaurant, caf and night club, is still the leading place of encounter for both clandestine contacts and prostit tes. The house or partment, nd hotel or rooming house have increased in relative frequency as places of exposure while tomobiles, brothels and

outdoors have decreased (recall seasonal factors). The brothel, which was the leading place of exposure for paid prostitutes in the 1942 series, is now in third place with hotel or rooming house first and home or apartment second.

With all the emphasis that has been placed on the importance of civilian cooperative effort, it will be clear that influence should precede pressure, and pressure precede force where the military and naval groups are convinced that civilian inadequacy underlies their excessive rates. Pressure consists in the repeated appearance and insistent repetition in the offices of the public health and other civilian authorities included in the "gang-up" of venereal disease control officers in uniform. Offers of cooperation in reporting, improved reporting, improved and intensified follow-up of unutilized reports, offers of witnesses for civilian-initiated repressive procedures (closing of liquor abuses, curfew and early closing laws, suppression of houses, repression of solicitation) are all preliminary steps. The next grade of pressure is the introduction with or without request of the civilian authority, but preferably with, of the Military Police and the Shore Patrol. The general practice is, of course, to turn over military personnel arrested by the civil authorities in compromising or vicious situations, to their local command, and the local civilian authority may not unreasonably expect assurance from the military that something is being done with such cases, and vice versa. The military authority may confidently point out to civil agencies by invitation or otherwise, conspicuous lacks in their attention to the leave situation and the protection and entertainment as a matter of patriotic duty, of personnel on leave or en route.

A next form of pressure and one preferably invoked by request rather than as threat and execution, is the out-of-bounds or off-limits type of order, which in present practice can issue from a variety of sources and cover small as well as large situations. This type of control is particularly exercised against districts, groups of establishments, individual establishments, and even regions along highways and so forth within the same local or state jurisdiction.

There exists also a separate Federal agency to which both civil and military authority can take appeal, and which proceeds to some extent also on its own initiative, though always seeking to cultivate local mechanisms and local sentiments. This is the Social Protection Division of the Federal Security Agency, whose organization and technic of procedure have been well described by its Director, Eliot Ness (Venereal Disease Information, 22: 456, December 1941). The Division is concerned with the protection of the community and particularly of its girls and young women, from prostitution and other related social hazards. It also stimulates the constructive treatment and care of girls and women detained by the police. In its long-term aspects it is an integral part of the total public welfare program of the country, and depends for its effectiveness upon the established agencies for public health, medical care, law enforcement, public assistance, recreation and child protection, and in turn supplements these agencies in its particular field. It devotes its energies particularly under four headings: repression of commercialized prostitution, the treatment of prostitutes including emphasis on rehabilitation, the protection of girls in defense areas, and cooperation with other agencies.

The May Act.—The big stick of venereal disease control by the armed forces was enacted as the May Act by Congress in July 1941. Confronted with an unalterable opposition on the part of the American public to the prohibition of alcohol, this act lacked at the start some of the most important

basic elements of control provided by the Selective Service Act of the previous war It came into existence late after many of the military and naval establishments were planned and quite fully developed it has a rather complicated mechanism of invocation within the armed forces themselves and places enforcement almost entirely in the hands of a badly over-worked agency the Federal Bureau of Investigation though its tremendous efficiency is fully recognized The result has been a relatively insignificant use of the act, and on these occasions mainly against important cantonment areas mostly in the South Its invocation is inevitably in contravention of the broadly constructive policy that action should be at the demand of local sentiment and with local support. Nonetheless, enactments such as the May Act are necessary evils, even though in their framing they may turn out to be jointed clubs.

Responsibility and Penalty —The armed forces have had to struggle with their special problems. The driving of venereal disease into concealment has been countered first by penalty in the form of forfeiture of pay (1912) for failure to take prophylaxis, as evidenced by absence of record of the fact in individuals developing infection This was reinforced by monthly physical inspection (colloquially but erroneously designated "short arm" inspection). During the period of World War I punitive regulation was supplemented by the placing of official responsibility on unit commanders for the venereal disease rates of their commands (1917) Towards the value of both of these measures, experienced students like Colonel Siler are distinctly inclined. Pappas rates the principle of responsibility of the unit commander as among the most fundamental in military venereal disease control On the other hand, there can be no denying that the trend of treatment toward shortened effective procedure and toward shortened but ineffective though symptom-concealing procedure (sulfonamides) is likely not only to nullify the inspection provision of compulsory practice but to make outside treatment and concealment of infection particularly easy as an escape from penalty This in its turn reacts on any attempt to make prophylaxis compulsory as revealed by the occurrence of infection in those who fail to seek it, and disturbs the entire mechanism of the use of station prophylaxis, the most effective instruments of venereal disease control in the catalogue. There is therefore an as yet undecided issue here which only subsequent experience can evaluate There seems reason to believe that the problem like all venereal disease control problems, has important local features and the nature of the command and locale, the character perhaps even the race of the troops concerned, the individuality of the responsible officers will make special solutions work at one point when they are ineffective at others. It is believed, therefore, that at this point particularly autonomy may well prevail under the aegis of the basic principle that the unit commander must assume responsibility for the venereal disease rate along with the general health standing and military efficiency of his command.

CHAPTER XXIV

THE CURRENT DEVELOPMENTS—PENICILLIN

The Pace of Discovery.—Two figures were coming into being as the third revision of this textbook was approaching completion—the one destined to become a giant, the other probably a dwarf. Intensive arsenotherapy was reaching its full stature in massive foreshortened treatment—its sole remaining drawback, toxicity. The promised (though not yet completely fulfilled) answer to toxicity is the advance of knowledge of the detoxicants, which can make the arsenic-heavy metal combinations safe. Just as safety seemed within reach, and arsenotherapy about to mount the giant's throne, a reactionless, safe antibiotic agent, penicillin, challenged its title to the sceptor. Though the rivals will for some time dispute the title, and the struggle perhaps end in a compromise arseno-penicillin handclasp, it is already growing clearer which will be the ruling giant, which the subordinated if not defeated dwarf. Even the drama of the occasion does not however, justify as yet calling the giant Penicillin the King. But at least we know that we can now cry "The king is dead—long live the King" and with this introduction, it will soon be possible for the reader to infer by space and type font, which way our personal beliefs on kingship are tending. His first problem then, is to decide how to conduct himself in the interregnum.

For the interregnum these reflections are suggested:

1. The established principles regarding syphilis and its behavior under treatment have not lost their meaning. Without them we might well be in a milling mob.

2. The arsenotherapeutic era warns us against the repetition of the serious mistakes of 1911–1920—the one-dose cure unachieved, the infectious relapse unrecognized, follow-up unknown, titered serologic tests as measurements of treatment response nonexistent, the spinal fluid warnings of asymptomatic neurosyphilis unsought for, neurorecurrence unforeseen, the variations in drug activity and behavior unsuspected, treatment allergy yet to be heard of, the causes and prevention of serious reaction guessed at, overlooked, slowly and painfully brought to light, with an irreducible residue of mortality confronting us almost until today.

3. The arsenotherapeutic era has set base lines and standards in curative and palliative performance in fractions of a per cent against which to measure new claims to therapeutic preeminence; has trained minds and organizations in logic, teamwork, planning and procedure, and in the evaluation of chemotherapeutic agents; has been combined with collateral methods (fever therapy for example) that will now in turn be integrated with the new discovery. It may be even so combined with the new to bring, for the first time, the one hundred per cent cure.

4. The arsenotherapeutic era has warned of the dangers of loose thinking—letting down the bars on standards, "pushing" a hoped-for result.

A short statement on arsenical detoxicants recently reported in the literature is given at the opening of this chapter.

5 The arsenotherapeutic era has taught, and it has in the same process set limits on the conclusive significance of time in the evaluation of results. Less than a lifetime now will decide the new order—less than a decade perhaps, because of what we know from the past.

6 For years to come there will be patients who have had the old treatment, whose decisions must be made for them on the basis of the old, plus the new

It appears then, that penicillin if and when enthroned, will literally climb to the seat on the shoulders of the sound, established and effective past of syphilotherapy And with these preliminary remarks we proceed to summarize the recent acquisitions in the field of the detoxicants.

Mode of Action of Arsenical Detoxicants.—For previous discussion of the subject of detoxicants, see Chapter IX. Among the more recently proposed detoxicants is, of course, ascorbic acid and its derivatives, which, as vitamin C, is assumed to have an influence on capillary fragility (as in scurvy) and upon perhaps the allergic state. McChesney Barlow and Klinck (1944) found not only that ascorbic acid, but other organic acids, including isoascorbic, d-gluco-ascorbic, lactic, pyruvic, succinic, malic, mandelic, aspartic, gluconic, β-ketoglucuronic acid and l-cystine, exercised a detoxifying effect on arsenical preparations. Significant protection was obtained in animals against the toxicity of neoarsphenamine. The effect is most favorable when the arsenical and the protective agent are injected intravenously in the same solution, but is nonetheless present when they are injected simultaneously at different sites. Ascorbic acid and para-aminobenzoic acid are of equal value as detoxicants for neoarsphenamine

Simultaneously with its detoxicating power must, of course, be considered the effect of the detoxicant on the spirillicidal action of the drug employed. Ascorbic and para-aminobenzoic acid and their congeners, so far as investigated, do not appear to rob the arsenicals with which they have been tested of their spirillicidal value, notwithstanding their detoxicating power The mode of action of detoxicants of this type is not yet clear The above-mentioned authors believe that most of the effect of the ascorbic acid is that of preventing oxidation, chiefly after injection. It is, of course, importa t further to find out whether a detoxicant acts by changing the affinity of the drug for tissue cells, which is offered by Hogan and Eagle (1944) as an explanation of the extraordinary differences in the toxicity of various arsenicals. It follows that the less toxic compounds and the more effective detoxicants prevent the linkage of the therapeutic agent with tissue cells and thus likewise make possible their rapid excretion.

The clinical application of para-aminobenzoic acid in protecting against the toxicity of trivalent and pentavalent arsenicals is only in its beginnings and the report by Rose, Travell, Solomon and Sandground certainly presents no convincing evidence of effectiveness so far as the methods tried are concerned Whether the knowledge accumulated in the animal in this group of detoxicants will be transferable to man remains to be seen.

Methyl Chalcone of Hesperidin.—This substance or group of substances act as an arsenical detoxicant by protecting against excessive capillary fragility which is assumed to underlie the most fatal of the grave complications of the use of the arsenicals, hemorrhagic encephalopathy

The substance is pparently an active ingredient of lemon juice and lemon peel, and was apparently shown by Warwa and Webb (1942) to decrease the fragility of capillaries and protect against localized hemorrhages. Methyl chalcone has been studied by Griffith (personal communication) with results apparently confirmatory of the capillary protective action, and Goldstein, Stolman, and Goldfarb (1945) applied the use of this substance experimentally to animals in combination with mapharsen. The results indicated a substantial protection of rabbits by the mapharsen-methyl-chalcone combination. These authors further showed that methyl chalcone of hesperidin does not impair the spirochetcidal activity of mapharsen in vitro. It was even suggested that the substance had some spirochetcidal effect over and above the action of the mapharsen.

Thus far no clinical report of the use of methyl chalcone of hesperidin in the treatment of syphilis has appeared.

PENICILLIN IN THE TREATMENT OF SYPHILIS

The Literature —It is not proposed here to review the already extensive literature accumulating about an antibiotic agent of such superb versatility as penicillin. Instead, the following references are cited for those who wish a

thorough-going and easily accessible review of the subject. A N Richards, as Chairman of the Committee on Medical Research of the Office of Scientific Research and Development (J A M. A. 122:235 1943) gives the early historical and clinical background with emphasis on the development of penicillin manufacture, investigation and use in this country The next authoritative statement is that of Keefer and associates of the Committee on Chemotherapeutic and Other Agents, Division of Medical Sciences, National Research Council (J A. M A 122 1217 1943) on whom was placed the responsibility for allocation of penicillin to medical investigators in the United States They described tersely the use of penicillin in the conditions in which it was to that date known to be effective. Syphilis was not studied, since the publication antedates the use of penicillin in syphilis by Mahoney and his co-workers An important symposium on the clinical use of penicillin and a discussion of anti microbial agents of biological origin (J A. M. A. 124:611–637 1944) presented the experience of Dawson and Hobby Herrell, Bloomfield, Rantz and Kirby and Dubos s analysis of the mechanism of action. This was followed in May 1944 by an excellent review of the literature through 1943 by Lieutenant G F Schmitt, M. C., USN(R) (Am. J Med. Sc., 207:601–678) with a bibliography of 126 titles which will give the average reader all he can absorb of technical detail, from culture media through therapeutics. This includes, however only a notation on the treatment of syphilis.

Because of the extremely important part played by the cooperation of the great pharmaceutical manufacturers of this country and their research laboratories in the development of penicillin manufacture, unusual weight attaches to the publications of these concerns on the subject. Any of the large well known pharmaceutical houses can be addressed by the physician for copies of brochures, collections of bibliographic references, news items and so forth, as may be desired.

Historical Summary —For those interested in dates, 1929 the year in which Alexander Fleming of London recognized the inhibitory effect of mold cultures upon cultures of staphylococci, can well compare with 1909 and 1910 which marked the Ehrlich-Hata Bertheim synthesis of "606" The discovery remained dormant for a time, 1932 being the date of confirmation of Fleming s discovery by Oxford investigators, and nine years elapsing between discovery and the making of penicillin available for therapeutic purposes, through the pioneering work of H. W Florey of Oxford and his associates. As pointed out by Richards (1943) Florey and Heatley s visit to the United States, under the auspices of the Rockefeller Foundation in 1941 marked the beginning of the tremendous wave of interest and productive activity which has set the United States, in all probability far ahead of the rest of the world in the manufacture and use of penicillin.

Because of the scarcity of the supply and the anticipated—and, in fact, demonstrated—tremendous importance of penicillin in the treatment of various types of war casualties, the responsibility for the development, manufacture and general allocation of penicillin has devolved upon the War Production Board. The currently available supply of penicillin devoted to investigative purposes has been under the control of the Office of Scientific Research and Development and the Committee on Chemotherapeutic and Other Agents of the National Research Council has, under the chairmanship of C. S. Keefer carried the responsibility for allocations to individual investigators and groups. After Mahoney and his co-workers had established the potential usefulness of

penicillin in the treatment of syphilis, the Subcommittee on Venereal Diseases of the National Research Council, under the chairmanship of Moore and subsequently a Penicillin Panel appointed by them, undertook the organization of a general program of study in the field of syphilis with allocations made for specific purposes to cooperating clinicians and their organizations throughout the country The plan of investigation for early syphilis involved a participation of 23 clinics working under allocated time-dosage schedules in the treatment of early syphilis, and 8 clinics with only general instruction, working on various aspects of late syphilis. The results, correlated and presented by

Fig. 896.

SEROLOGIC RESULTS OF PENICILLIN TREATMENT

Case 1—L.W.—Number 116769 Duration of Disease—9 Days

Time after start of therapy	Qualitative Methods: Super sens. Kline excl.	Mazzini	Diagnostic flocculation: Kline diag.	Kahn stand.	Hinton	Eagle	Comp. fix. Kolmer simp.	Quantitative Methods: Diagnostic flocculation: Mazzini	Kahn	Comp. fix. Kolmer
Days										
0		4		4	Pos.	Pos.	4	44421	4442±	444444
1		4		4	Pos.	Pos.	4	44421	4442±	44443
9	4	4	4	4	Pos.	Pos.	4	44442	44441	4442
23		4		3	Pos.	Pos.	4	432	441	4443±
30	4	4	3	3	Pos.	—	4	4442	4431	442
37	4	4	1 Dbt.	2	Dbt.	—	3	4431	41	[illegible]
44	3	4	—	1 Dbt.	—	—	4	442	4±	443±
51	1 Dbt	4	—	—	—	—	4	42	1	4441
58	1 Dbt	4	—	—	—	—	—	43	1	
65	2	2 Dbt	—	—	—	—	—	21		
72	1 Dbt.	2 Dbt.	—	—	—	—	—	21		
80	—	2 Dbt.	—	—		—	—	2±	±	
86	—	2 Dbt	—	—	—	—	—	2		
93		1 Dbt.	—	—	—	—	—	1		
Months										
4		—	—	—	—	—	—			
5	—	—	—	—	—	—	—			
6		1 Dbt.	—	—	—	—	—			
7	—	—	—	—	—	—	—			
8	—	—	—	—	—	—	—			
9		—	—	—		—	—			
11	—	1 Dbt.	—	—	—	—	—			—

Courtesy of Dr John F Mahoney Senior Surgeon, U.S.P.H.S. Research Center Stapleton, Staten Island, New York.

J E. Moore for early syphilis, and John H Stokes for late syphilis, at the American Medical Association meeting in Chicago, June 1944 will be referred to subsequently as the Panel Research of the Office of Scientific Research and Development and the Committee on Medical Research

Penicillin in Syphilis.—The distinction of discovering the applicability of penicillin to the treatment of syphilis belongs incontestably to J F Mahoney Senior Surgeon United States Public Health Service the head of the Venereal Disease Research Center at the United States Marine Hospital, Staten Island, who with his associates R. C Arnold and A. Harris, published their original paper in December 1943 (Am J Pub Health 33 1387 and Ven. Dis. Inform.

24:355–357) Subsequent brief descriptions of the effect of penicillin on certain aspects of syphilis were later published by O'Leary and Herrell (Proc. Staff Meet., Mayo Clin. 19:20 1944) and by Bloomfield, Rantz and Kirby in the Symposium referred to above (J A. M. A. 124:927 1944)

Mahoney and his associates, after finding by limited animal experimentation that penicillin possessed spirillicidal activity for *Spirochaeta pallida*, transferred the work to man, because of the known lack of toxicity of the antibiotic agent. The early results in the animal phase of the general study to quote the authors, indicate that the time-dose relationship will prove to be as important in this therapy as in the use of other chemotherapeutic agents. Their four original patients were all males with characteristic *Spirochaeta pallida* identified by darkfield from single penile ulcers. Mahoney's method of studying the serologic behavior of the case by a battery of tests in which the gradual decline of intensity of reaction to negative over a period of observation could be observed, is well shown in his historic Case 1 whose chart is reproduced as Figure 896 The spirillicidal action of penicillin (*Spirochaeta pallida* disappeared by the sixteenth hour) the occurrence of Herxheimer-like reactions and the healing of lesions were coincidently demonstrated.

O'Leary and Herrell's case was that of a woman with a late syphilid of the nose and a concomitant neurosyphilis who was treated with penicillin by the continuous intravenous drip in contrast to the intramuscular route employed by Mahoney and the total dose was approximately one-fourth that employed by Mahoney Healing of the late syphilid and slight improvement in the spinal fluid were observed over a period of about six weeks. Bloomfield, Rantz and Kirby treated seven cases of early syphilis by intravenous drip with total doses approximating 1,000,000 Oxford units. Their findings confirmed Mahoney's observations with regard to spirillicidal and Herxheimer effect.

Against this background we now see projected the evaluation study brought to an admittedly only preliminary report, by the Panel Research summaries, spokesmanned by Moore and Stokes at the American Medical Association, in June, 1944 to which fuller reference must subsequently be made. As a preliminary to any comprehension of penicillin in the treatment of syphilis, Figure 897 attempts to summarize what the practitioner meeting this antibiotic agent for the first time should have as elementary informational equipment.

The Known and the Unknown on Penicillin in Syphilis.—It is now in order to place penicillin, so far as present knowledge permits, in the therapy of syphilis. This has been attempted in a manner to indicate so far as may now be anticipated, both the known and the unknown (Fig 898) It may of course, be anticipated that other penicillins or relatives of penicillin will come into existence. At the present time, only three of the relatively large group of antibiotics appear to possess spirillicidal activity but once the structural formula of penicillin becomes available and its synthesis is possible it may be anticipated that the chemotherapeutic history of the arsenicals, with its shifts of important elements and groups within the molecular structural formula, will repeat itself

Outstanding Problems in the Advent of Penicillin.—It hardly seems, with the goal of therapeutic efficiency if not absolute mastery of the infection by a reactionless agent, in sight, that any significant desirata remain. This, unfortunately is not the case. As intimated at several points in the discussion the present technics of penicillin administration leave much to be desired from the standpoint of the control of syphilis as a public health problem. The simul

Fig. 897

PENICILLIN FOR THE PRACTITIONER

A General Statement of th Facts

1 Produced by a fungus, *Penicill um notatum*, in amounts varying with strain, the extract used therapeutically is a partially purified product, the sodium, calcium or ammonium salt of the base, yellow powder "Pure penicillin is not vailable as yet. Pyrogens must be removed i manufacture.

2. Therapeutic activity is measured by th Oxford unit," an amount of penicillin capable of inhibiting to a defined degree the growth of a strain of *Staphylococcus aureus* Standard maintained and manufacturing quality controlled by the Federal Food and Drug Administration in the United States. The Oxford unit will probably be replaced by weight measurement of dosage of 1650 O.U. per milligram.

3. Manufactured by a number of concerns, there are discernible differences in lot behavior marked differences in price and undefined differences in potency Expiration dates are well inside the probable lif of the preparation.

4. Marketed in mpules in vacuo, i amounts of 5,000, 10,000 25 000, 100,000 and 1,000 000 O.U thought to be thermolabile (ceiling of 4 C.) but less so than nticipated, the sodium salt is easily soluble in distilled water physiologic salt solution, 5 per cent glucose. The first scheme is used in intramuscular the latter two i intravenous work. Calcium penicillin follows the same rules, more stable, rated as equal to sodium penicillin in effect.

5 For intramuscular injection, 50,000 O U can be administered in 1 cc. of water Potency of solutions at room temperature shown t be maintained for four days with current preparations (Kirby 1944) making icebox storage of solutions unnecessary but of ampules still desirable. One day supply may be mixed in summer

6. For intravenous injection, use 1,000 to 5,000 O.U per cc sterile saline For drip, 25-50 O.U per cc. of saline or 5 per cent dextrose solution.

7 Oral administration ineffective (destroyed by HCl), enteric coating erratic duodenal tube, wkward, not used destroyed in colon by an antagonistic substance. Subcutaneous absorption slow large loss. Inunction for topical use only Not advised for systemic therapy

8. Penicillin is poor tissue penetrator Eliminated rapidly largely by the kidneys (58 per cent first hour), most rapidly after intravenous, slower fter intramuscular injection Methods of biologic ssay so far have too large a margin of error for over-positive statements regarding blood levels, presence or absence of minut amounts.

9. A method of delaying the elimination of penicillin by the administration of p-amino-hippuric acid has just been reported (experimental in rabbits) (Beyer Woodward, Peters, Verwey and Mattis, Science 100 107 Aug 4 1944)

10 Because of rapid elimination, administration is currently by drip or intramuscular injection repeated t three-hour intervals round the clock, thus necessitating hospital or continuous nursing ttention. The total dose is fractioned mong the scheduled periods, usually equally but in some cases with initial reduction (in syphilis, to void Herxheimer effects) Inter jection intervals as long as twelve hours have been used, foreshadowing an ambulatory techniq (not yet recommended)

11 In defining penicillin dosage give in th following order the total Oxford units (or milligrams if sed when standard is made official); the fractioned dose per injection, the time interval between injection the time of the entire course or series; the route of administration. These facts with manufacturer name and lot number should be part of ll records. The same manufacturer product, if possible should be used in given case

12. In intravenous injection technic with slight risk of thrombosis the needle can be strapped but the drip technic (p. 317) is preferred. Give the first 200 cc rapidly then reduce rate t 30 t 40 drops per minut (dextrose).

13. In intramuscular injection technic, follow procedure of Chapter VIII (p. 304). Vary injection sit divide mounts over 2 cc. between the two buttocks; can be given subscapularly or into thigh or deltoid but not advised. Slight burning usually only reaction but in rare idiosyncrasy (probably due t impurities) or allergy may be deeply swelling. Moderate exercise promotes absorption; need not be urged.

Fig. 807 (*Continued*)

PENICILLIN FOR THE PRACTITIONER

A General Statement of the Facts

14. For intrathecal administration (intraspinal, intracisternal) 5,000 units per cc., 10,000 units per injection, once or twice daily (Bloomfield)
15. Reactions to penicillin are few and trivial and are suspected of being due to impurities. Do not confuse Herxheimer or therapeutic shock effects in syphilis. Allergy appears in workers in manufacture but thus far not clearly recognized in treatment (urticaria, "id" reactions on palms, eosinophilia of 20 to 30 per cent, exfoliative dermatitis, 2 cases) The commonest general reaction is urticaria with severe itching lasting 2 to 5 days (1 to 5 per cent of patients) with or without marked gastro-intestinal symptoms, not recurrent with retreatment or change of lot and manufacturer Fever with or without chills, headache or head-flush, tingling sensations in testes, skin burning, paronals, may occur While study of animals is not complete, visceral or vascular or nervous tissue injury has not, so far been recognized at therapeutic dosage in man.
16. Herxheimer or therapeutic shock effects occur in human syphilis at approximately the same time and with symptomatology to correspond with the expectancy for the trivalent arsenicals. See p. 240 The cutaneous eruptive exacerbation is less common than with the arsenicals.

taneous effect of the antibiotic on the gonococcus and *Spirochaeta pallida* introduces, along with the suggested advantage of a one-method treatment for two diseases, the rather serious problem of under treating syphilis in its initial stages, concomitantly present with gonorrhea A technic will have to be devised with probable emphasis on the syphilis follow-up of gonorrheal patients which will keep the masked syphilis from slipping through, to go on to infectious relapse and recurrence.

The existing intramuscular and intravenous technics for the use of penicillin in syphilis are unwieldy and require an amount of supervision that will, for a long time make them impractical for the large proportion of infected individuals, except at suitably equipped centers, until an ambulatory procedure is developed Whether this will stem from the possible feasibility of longer intervals between intramuscular injection whether it will arise from the development of new penicillin compounds of higher efficiency or different rates of absorption from the simple salts now available or whether it will be accomplished by the use of absorption-delaying vehicles or elimination-delaying agents, remains to be determined. When the patient can visit the doctor office once or perhaps twice in the twenty-four hours, the sun will be rising on the future of syphilis control by penicillin, though it will be setting behind the hard-worked doctor s back.

Mahoney has frequently stated informally that he anticipates the return of the treatment of syphilis from the hands of experts and organizations, to the office of the general practitioner In a speculative mood one might go even further than this, and imagine himself at the day when a "protamine-penicillin" will be administered at the start by the office nurse and throughout the continuance, to the finish of treatment by the patient himself Certainly physicians will no longer need to lay bare the embarrassment of their own conditions to their professional brethren, for few will lack the hardihood to carry out their own penicillin therapy

The Cost.—As this discussion is written, it will be difficult to apply penicillin on a large scale to the syphilis of clinic practice, and the common run of mankind. The price per hundred thousand units, ranging from about $4.00 to

Fig. [illegible]

PENICILLIN IN SYPHILIS

The Known and the Unknown as of July 1944

The Known	The Unknown
1. Spirillicidal *in vitro* and *in vivo*.	1. The mechanism is unknown; assumed from bacterial analogies to consist in (1) inhibition of multiplication, (2) direct action on a synthetic anabolic process within the spirochetal cell (as with sulfonamides [Dubos, Weiss 1944]) It is not a bacteriolysis as with phage.
2. Spirillicidal at all dosages clinically explored in man from 1 000 to 25,000 O U every 3 hours intramuscularly	2. The spirocheticidal dose bears no known relation to the curative dose (animals)
3. Organisms disappear from surface lesions in 6 to 60 hours, usually 12 to 24 hours at 25,000 O U	3. The clinical significance of the shorter and longer periods as compared with dosage is still unknown.
4. No penicillin-resistant organisms have been encountered as yet in man. Suggested in animals (Dunham, Hamre, McKee and Rake 1944)	4. Will penicillin resistance appear later? Will it be overcome by modification in dosage technic (*i.e.* shorter time intervals, larger single or total dose repetition, adjunct treatment with arsenicals, bismuth, fever)?
5. Treatment resistance is foreshadowed by serologic curves in certain patients.	5. Where no response is shown, has the patient a metabolizing defect (inability to utilize the penicillin) or a penicillin-resistant spirochete
6. A flare, Herxheimer or therapeutic shock effect follows the first administrations, about the time it occurs with the arsphenamines. Evidenced in blood serologic titer and cerebrospinal fluid as well as lesions and clinical symptoms.	6. Does this justify inference as to a delayed action intermediary mechanism between penicillin and the organism, as inferred by some for the arsenicals?
7. Therapeutic paradox is suspected but not proved.	7. What effect will it have on cirrhotic livers, early syphilitic aortitis, coronary disease?
8. *Penicillin follows the old rule—the* earlier in early syphilis treatment begins, the better the result. It is more effective in seropositive primary syphilis, than the arsenicals, by first reports.	8. *Can it be inferred from this and from* spirillicidal action and Herxheimer effect that penicillin can be thought of as an arsenical or superarsenical in the schemes of early syphilis treatment?
9. Results in early syphilis are demonstrably better the higher the dose (information up to 1,200 000 O U in 8 days) On trial are dosage schemes of 1 200,000 in 4 days, 2,400,000 in 8 days, 100,000 to 50,000 O.U. twice daily for 8–12 days.	9. The actual curative dose by weight is unknown.

Fig. 808 (*Continued*)

PENICILLIN IN SYPHILIS

The Known and the Unknown as of July 1944

The Known	The Unknown
10. Present information indicates that intramuscular administration is 5 to 6 times more effective in early syphilis than intravenous (range of 600,000 to 1,200,000 O U.) judged by relapses (Moore for Panel Research)	10. Is blood level maintenance important or is succession of peaks or spikes as satisfactory as continuous high level? Can an absorption-slowing vehicle or combination produce and prolong blood level spike, thus simplifying the round-the-clock frequency of aqueous solution injections? How far apart, with adequate individual doses (50 000 O U up) can injections be spaced? Can more rapid and sensitive blood level determination technic be found?
11. The accepted safe dose for early syphilis is not less, for the moment, than 2,400,000 O.U in 8 days. Proposed by Mahoney (USPHS) this is now Army-Navy standard. In early syphilis give maximums, not minimums. The time interval between doses has considerable elasticity not yet determined.	11. How large an amount will cure all or the nearest to all, is the needed knowledge—not how many how little will cure. Very little or none will cure some.
12. The penicillin relapse rates in early syphilis are thus far no greater or somewhat less at 1,200,000 O U. than in either standard combined, or in massive dose or other intensive arsenical-bismuth systems.	12. By what combination or intensification will this refractory margin be done away with, separating us from the 100 per cent cure—penicillin-mapharsen, penicillin-bismuth penicillin-fever; penicillin at higher dosage, shorter or longer intervals, for shorter or longer periods?
13. Penicillin-mapharsen (60,000 and 300,000 O U. plus 320 mg mapharsen in 8 days) has good record so far on both safety and relapse.	13. Do such combinations affect either therapeutic activity or reactivity of either agent—and do therapeutic activity and toxicity increase in different ratios?
14. Rabbit syphilis results so far indicate (a) single huge doses do not cure. (b) Repeated large doses at short intervals do not cure. (c) Repeated moderate or large doses at longer intervals over a longer period, do cure. Retarding vehicles (oil) require much larger doses, individual and total, for cure.	14. Does this mean that penicillin therapy will observe the arsenic-heavy metal principle of standard treatment days, that prolongation (of treatment) is as important as mass?
15. Treatment can be repeated if relapse or spontaneous recurrence in early syphilis occurs, at an equal (1,200,000 O U. or over) or larger dosage, with renewed response in most but not all cases but no decision yet on complete effectiveness.	15. Will such retreatment lead to an ultimate residue of penicillin-fast cases, to be avoided by huge initial treatment or much more prolonged moderate or high dosage treatment than at present in use? (See 14.)

PENICILLIN IN SYPHILIS

The Known and the Unknown as of July 1944

The Known

16. Penicillin shows signs of controlling malignant precocious tertiarism and arsenic-heavy metal treatment resistance.

17 Penicillin will reverse abnormal spinal fluids, even of Grade III in an undetermined proportion of cases to normal by total doses from 1 200,000 to 3,000,000 O U in single or 2 repeated sessions even after large amounts of standard treatment over long periods have failed. Standard treatment previously given does not seem to increase response to penicillin in late syphilis.

18. Under adequat (1,200,000 to 4,000 000 O U) dosage, penicillin continues to have clinical and serologic good effect for some time after the short courses are stopped. (Up to about 4 months?) Early relapse, especially mucocutaneous, begins to appear in about 90 days.

19 In early syphilis associated with pregnancy treated with 1 200,000 O U in 8 days (Lentz, Ingraham, Beerman nd Stokes) it is known that ( ) the *spirillicidal and lesion-healing effect* of penicillin i the same in other early syphilis (*b*) the child is adequately protected apparently (or cured) in large proportion of the few cases so far studied (born and remains seronegative or becomes so after birth) The mother serologic curve behaves as in early syphilis in general, but there is suggestion of *relapse tendency in some cases following childbirth* (observation period too short). No spirochetes so far found the umbilical vein scrapings. Penicillin in the umbilical vein blood after large dose given the mother *just before onset of labor* (Barksdale). Risk of inducing abortion (placental shock?) small but real, voidable by reducing initial dose.

The Unknown

16. Does penicillin insufficiently used (say below 600,000 O.U) induce immediate ( ) treatment allergy or *Unstimmung* as in malignant precocious tertiarism; (*b*) neurorecurrence (*c*) predispose t any type of late involvement over a longer period (questions raised for the arsenical in neurosyphilis)?

17 Will this mean control and prevention of neurosyphilis when applied in early syphilis? What is the optimum system for such effects—high initial dosage single course (2,400,000 O U or over up to 4,000,000 O.U. so far) or repeated less intense courses (not less than 1,200,000 O U each)? Will they be enhanced by simultaneous penicillin-mapharsen, penicillin-bismuth and penicillin-fever If the penicillin is ( ) reduced below 1,200,000 O U, or (*b*) held at 1,200,000 O.U or (*c*) raised to 2,400,000 O U or over? Do these combinations alter the action of penicillin, how and when is time relationships of the combination?

18. How long does the curative impetus last at various doses nd time schedules (*a* in intensive arsenotherapy malaria) and in various stages and types of the disease? Will penicillin be effective in preventing cardiovascular and visceral well as neurosyphilis, including especially so-called progression under treatment?

19. More time required to answer the questions involved. Is the adequate dose *for the mother-child combination* not larger even than the 2,400,000 O U *dose now ad ised for early syphilis?* Is the mother and child combination (in tero) curable easily as non-pregnant woman, or woman as easily (or more easily) the man. Where does the protection of the child take place; *i.e.* cure of the mother cure of child by mother (no penicillin in child?)? What effect has stage of beginning treatment in mother? What will be the results of treating pregnant women with latent syphilis. Does the child in tero help protect and treat" the mother (liter rise or relapse in mother blood after delivery)? I the placenta a penicillin barrier?

Fig. 898 (*Continued*)

PENICILLIN IN SYPHILIS

The Known and the Unknown
as of July 1944

The Known	The Unknown
20. Penicillin if used with caution at the start to avoid Herxheimer effects, produces rapid symptomatic improvement in congenital syphilitic infants, with roentgenologically demonstrable effects on epiphyseal and other bone lesions. The dose used thus far is the weight equivalent of an adult dosage of from 1,200,000 to 2,400,000 O U in 8–10 days, intramuscularly	20. Will it cure outright and in what proportion Will there be therapeutic paradoxical effects, especially in hepatosplenic involvement?
21. Penicillin heals late benign syphilids of the skin, mucosae and skeletal system at least as rapidly as the arsenicals but at a dosage (200,000 to 400,000) much too low to influence graver concomitant types of syphilis (e g neurosyphilis, especially Type III spinal fluids)	21. How much of the effect, e g on old osteomyelitis, is action on the pyogenic secondary invader rather than the primary syphilitic process?
22. Penicillin in late congenital syphilis (interstitial keratitis) acts equivocally sometimes dramatically favorably about as often disappointing. No dosage scale seems to give consistent results. Fever combinations may fail or succeed without rule. Other manifestations not yet reported.	22. What is the complex mechanism back of interstitial keratitis? Is the allergic factor important? The collateral infective or intoxicative factor?
23. The action of penicillin in latency and serologic fastness and in cardiovascular syphilis has not yet been studied	23. Experience opposes the expectation of more than "life insurance protection and 20–30 serologic reversal in such material.
24. Action of penicillin in neurosyphilis is separately summarized (see pp. 1260–1261)	24. Does penicillin penetrate the nervous system? Is intrathecal therapy preferable to intramuscular and intravenous? What is the status of fever penicillin combinations? All unanswered questions as yet.
25 Penicillin seems likely (*a*) to displace the arsenicals entirely if penicillin bismuth system proves effective. (*b*) It may displace all existing agencies for syphilis treatment (including massive dose systems) if the proportion of treatment failures after one year equals or falls below the massive dose and foreshortened arsenic-heavy metal systems, including equal effectiveness in preventing asymptomatic neurosyphilis.	25. How soon should the shift to penicillin be made? What will penicillin-bismuth do? (Safer than arsenic.) Will the penicillin-fever combination (drip technic) single or repeated, shorten and improve results? Will clinic and expert management become unnecessary (granted an ambulatory or office technic develops)? Will the patient learn to treat himself (à la insulin)? Can it be made usable by mouth? Can it develop prophylactic usefulness, local or systemic? How identify masked syphilis in cases cured of gonorrhea, leaving the underlying and developing syphilis insufficiently treated?

Fig. 808 (Continued)

PENICILLIN IN SYPHILIS

The Known and the Unknown
as of July 1944

26. Penicillin will not do the impossible—resolve scars or their effects; rebuild structural and functional wrecks; restore lost neurons; perform miracles in complex processes heretofore known to be erratic in response to treatment and involving metabolic, allergic, psychosomatic and other factors uncorrected or yet unknown or unexplored

FROM A.D. 1943 IT WILL TAKE A YEAR TO GUESS, TWO YEARS TO INTIMATE, FIVE YEARS TO INDICATE, A DECADE OR MORE TO KNOW WHAT PENICILLIN DOES IN SYPHILIS

$10.00 of the antibiotic alone, the cost for the present "standard" "cure" of 2,400,000 O U will be nearly a hundred dollars before any professional or clinical overhead has been considered. Notwithstanding the enormous increase in production of penicillin and the rapid drop in price, it will not be until the cost stabilizes at or below $2.00 per hundred thousand units, that it will be possible to discuss with the lower fee level private patient a satisfactory handling of his case at figures current in the present arsenotherapeutic regimen.

Problem of Partially Completed Arsenotherapy.—What to do with patients who have begun or partially completed treatment for an early or a late syphilis by standard arsenical and heavy metal methods will soon become a question. Those who demand and can pay for it, will doubtless receive penicillin in a dosage adequate as experience develops, to the type of infection they presented at the start. It will be some time before the worth of the previous arsenotherapy as a preparation for or a hinderance to the efficiency of the superimposed penicillin can be determined. Penicillin can now conceivably be substituted for repetitions of arsenic-heavy metal therapy of various types, and especially for the massive dose or intensive systems. Such a transition will probably take place with developing knowledge during the next two years, as the results of Penicillin Panel research are evaluated and published. It would seem that the hazardous methods of arsenotherapy should go first.

Penicillin in Latency.—A leading question too is that of the place of penicillin in the treatment of the overwhelming burden of monosymptomatic seropositive latency which constitutes seventy per cent of the load problem of public health treatment practice. On this, at this writing, little knowledge exists. The determination of what the older treatment did to improve the outlook of the latent syphilitic, as conducted by the Cooperative Clinic Group under the supervision of Moore was, within the limitations of the material, a masterpiece of rationalization. Only years of examination and reexamination of a stabilized material by a stable group of investigators following an initially planned series of schedules will provide the scientific answer to such a problem. Meanwhile we may anticipate all manner of unscientific approaches, beginning in all probability with the administration to every demonstrably latent syphilitic who can afford it, of the 2,400 000 O U dose of penicillin as for early syphilis. It will be a long time before any basis for the reduction of this maximum dose will appear as has indeed been the case in CCG USPHS standard-

ization of the treatment of late latency Early latency (first four years of the infection) may properly be considered eligible especially for the maximum penicillin dosage appropriate to early syphilis.

It is impossible to overemphasize, and it must be iterated and reiterated, that our basic knowledge of penicillin has the qualities of Swiss cheese—more holes than substance in many particulars. For example, it may appear as penicillin-treated persons are subjected to general medical study and go on with life that functional changes have occurred in important organs which have limited recuperative power One need only recall the lag in the study of the behavior of the liver under arsenotherapy to realize the importance of such considerations in the background.

The Importance of Follow Up.—As a final point for emphasis as penicillin moves to the front of the stage, the problem of follow-up deserves critical attention. Lacking even the impress upon his sense of responsibility made by the five-day drip and ten-day to twelve-week multiple injection methods, it will become more difficult than ever before to induce the quickly treated patient to let us evaluate penicillin results, and to control relapse and recurrence, with the inevitable continued dissemination of the disease. The problem of follow up was clearly recognized by the Penicillin Panel Research group, and already experience clearly shows that except under extraordinary precaution, effort and efficiency lapse and loss of supervisory contact may amount to 35 to 45 per cent of cases treated. If penicillin fails to hold its present creditably low record of mucocutaneous serologic relapse even under the higher dosage systems, a situation may well be created with respect to syphilis, comparable to that predicted by Pelouze and other authorities for gonorrhea, as a sequel of the sulfonamide regimen. This makes the more pressing the systematized study of larger dosage and therapeutic combinations of superior effectiveness in the research program of the present moment. It also strengthens the demand for adequate follow-up organization in clinics, adequate provision of follow-up service by the health authority for the practicing physician who may fall heir to this material, and adequate contact-tracing service to find and bring in for study as well as treatment, the new infections whose source may be the unrecognized penicillin failure.

In fact, while indulging in predictions, we may confidently venture another—that contact-tracing will grow rather than diminish in importance in the epidemiologic control of the disease. As public health experience increasingly demonstrates, the mere therapeutic abolishing of the problem of infectiousness does not solve the whole problem of the transmission of venereal diseases. Venereal disease, and conspicuously syphilis, is transmitted at two times in its course when the patient is out of therapeutic control—namely before he knows he has the infection, and after he believes himself cured or has been told that he is cured. Neither of these epochs in the transmissibility of the infection can be wholly reached by a spirocheticide though, of course, increased spirochaticidal permanence, so to speak, relieves the load of the second period of transmissibility Here, then, one sees penicillin face to face with the bed rock of venereal disease control only to find that it is not the drug or the antibiotic, but the struggle with sexual promiscuity that seems to be the ultimate determining force in the elimination of the venereal infections. The public health venereal disease front is shifting from treatment control to promiscuity control (see Chapter XXIII)

THE PENICILLIN PANEL RESULTS

It seems advisable in substantiation of some of the summarized material in the text figures, to quote directly from the Penicillin Panel Research reports of Moore Mahoney Schwartz, Sternberg and Wood on early syphilis, and Stokes, Sternberg Schwartz, Mahoney Moore and Wood on late syphilis, as published in the Journal of the American Medical Association. Since neurosyphilis holds numerical preponderance in the series and is by all odds the most important aspect of late syphilis clinically two summaries will be given in Figures 900 and 901 on penicillin in neurosyphilis, preceded by a résumé of general serologic effects (J.A.M.A 126 63-80 1944)

THE TREATMENT OF EARLY SYPHILIS

Early Syphilis.—The report on early syphilis by the Penicillin Panel contains important specific statements. Early syphilis was under investigation at the time of presentation of the report in 23 clinics and research centers, whose names are given in the published account. The material was limited to patients in whom *Spirochaeta pallida* could be demonstrated indubitably in active lesions. The five variables of route of administration; interval between injections, duration of treatment total dosage; and possible combinations of penicillin with other drugs, were dealt with by holding the first three factors constant, all cases being treated by the intramuscular route every three hours day and night to a total of 60 injections given intramuscularly in seven and one-half days. Four treatment schedules provided 20-fold dosage range. In a later investigation the time-variable was studied and systems calling for 300,000, 600,000 and 1,200,000 O U. in 30 intramuscular injections over a four-day period, were employed, but the results are not yet available. The total number of cases at the closing of the books of the Penicillin Panel on May 9th, 1944, was 1,587 patients with early syphilis, of whom 1,418 had records suitable for punch coding and machine statistical analysis.

The results of this study of early syphilis emphasized over and over the importance of adequate dosage. While, with total doses of 300,000 units and up, healing is as rapid or more rapid than with the arsenicals, and a trend towards serologic reversal begins within a period of about twenty days after the start of treatment within the entire range from 60,000 to 1,200,000 O.U., the evidence clearly indicates that less than 600,000 units should not be used in the treatment of early syphilis that this dosage is inadequate to display the best efficiency of penicillin, and that doses of 1 200,000 O U and over should be regarded as a starting point for practice subsequent to this report. The rate of serologic reversal is stated by Moore to be identical with that observed after arsenotherapy whether with an arsphenamine given at weekly intervals, or mapharsen given by various intensive methods Temporary positives are observed in some cases of originally seronegative primary syphilis, with reversion to negative. Within the brief observation period of this study serologic results are said to have been satisfactory in 93.9 per cent of seronegative primary syphilis. The efficiency of the mapharsen-penicillin combination has been mentioned in Figure 898 The incidence of relapse interpreted by rigid criteria with reference to reinfection and including serologic relapse is thus far the only measure of efficiency of penicillin. Clinical and serologic relapses occurred in 92 patients with seronegative primary syphilis in 3.8 per cent. In seropositive primary syphilis the incidence of clinical and serologic relapse was 6 per cent and in early secondary syphilis nearly 10 per cent. The relapses occurred as early as 29 days and as late as 291 days after the start of treatment with penicillin. Moore has stated informally that it occurred around the ninety-day observation period. Intravenously administered penicillin was shown by this study to be clearly less effective than penicillin by the intramuscular route.

Moore and his collaborators reported on the results of treatment in special forms of syphilis as follows of 13 patients with early syphilis who had positive spinal fluids before treatment, 11 of Group II and 2 of Group III showed improvement or disappearance of the abnormalities in ten to fifty days in 10 of the patients and no improvement in 3. In 10 cases of acute syphilitic meningitis, the majority treated with 1 200,000 O U in seven and one-half days, dramatic symptomatic relief occurred in all, and in the majority the spinal fluid abnormalities had disappeared or were rapidly improving Eight patients with treatment-resistant persistent dark-field positive cutaneous syphilids, persisting in spite of metal chemotherapy responded promptly to penicillin and behaved serologically as did patients with previously untreated early syphilis. Twenty infants with early congenital syphilis, treated in the majority of cases with 40,000 units per kilo body weight, corresponding to a total dose of 1,200,000 units in the adult, showed clinical and serologic responses analogous to those of acquired syphilis in the adult.

THE TREATMENT OF LATE SYPHILIS, CONGENITAL SYPHILIS AND NEUROSYPHILIS WITH PENICILLIN

It will be recalled that O'Leary and Herrell observed in their patient with concomitant late cutaneous and asymptomatic neurosyphilis, the healing of the cutaneous lesions and improvement in cell count, colloidal tests and total protein in the spinal fluid; changes subsequently shown by the Panel research to be among those characteristic of the effect of penicillin in neurosyphilis, as indeed it has been more or less characteristic of all forms of treatment capable of influencing neurosyphilis. Mahoney (personal communication) had observed in badly debilitated patient with paresis, treated early in his experience, most striking symptomatic improvement following the use of penicillin.

Fig. 880

PENICILLIN AND THE BLOOD SEROLOGIC REACTIONS

1. Some reduction in strength of serologic reactions is almost always obtainable by penicillin total dosage from 300,000 units up.
2. Effect more marked with higher titers.
3. A provocative increase in titer may be followed by drop, often seen in initially sero-negative primary syphilis about to become seropositive.
4. In early syphilis the curve of decline to normal under massive dose penicillin (1,200,000 to 2,400,000 O U) in eight days compares with that of massive dose arsenotherapy or is even more rapid. A patient with strong positive after ninety days is candidate for retreatment.
5. In late and latent syphilis, decline in titer occurs in from 30 to 60 per cent of cases, and provocative effect in 20 per cent. Up and down fluctuation occurs and the effect of penicillin serologic fastness is still unexplored.
6. A consistent rise in serologic titer after consistent decline is warning of relapse or non-cure, as with the arsenicals.
7. Improvement in blood serologic reactions tends to parallel spinal fluid improvement, though not necessarily so; and symptomatic improvement may occur independent of any improvement in the blood. Improvement in the blood may occur independent of any symptomatic response.
8. Complement fixation and flocculation tend to parallel each other in the serologic response of a test battery.

SEROLOGIC PRINCIPLES APPLICABLE TO As-Bi THERAPY SEEM TO FIT PENICILLIN ALSO

It was quickly established by the Panel Research that in gummatous manifestations of the skin, mucosae and bones, the action of penicillin is so striking and complete that it seemed unnecessary to collect larger material for the moment than the 21 cases provided by the cooperating clinics.

It was clear, insofar as the material covered the question, that satisfactory healing occurred in benign late syphilis with doses too low to have adequate therapeutic effect on important con-

The eight clinics cooperating in the study of late syphilis included those of Bellevue Hospital (Evan Thomas, M.D.), the Boston Psychopathic Hospital (Harry P. Solomon, M.D.), Cornell University (Walsh McDermott, M.D.), Johns Hopkins University (J. E. Moore, M.D.), the Mayo Clinic (P. A. O'Leary, M.D.), the University of Michigan, (U. J. Wile, M.D.), and the University of Pennsylvania (John H. Stokes, M.D.). Of these Johns Hopkins University and the University of Pennsylvania have been longest in the field, and provided the largest and longest observed material. At the University of Pennsylvania the work was organized on a subpanel basis with the cooperative participation of the following individuals and clinical departments: J. H. Stokes, M.D., H. Beerman, M.D., N. R. Ingraham, Jr., M.D. and J. W. Lentz, M.D., Institute for the Control of Syphilis and Department of Dermatology and Syphilology; V. S. Wammock, M.D. and O. M. Carrozzino, M.D., Division of Venereal Disease Control, Philadelphia City Department of Health and Philadelphia General Hospital; Service B, Pennsylvania Hospital, G. D. Gammon, M.D. and D. Scott, Jr., M.D., Department of Neurology; Willard Steele, M.D., Department of Ophthalmology; F. H. Adler, M.D., Professor; J. I. M. Scott, M.D., E. K. Rose, M.D. and H. H. Perlman, M.D., Department of Pediatrics and Children's Hospital; Joseph Stokes, J. M.D., Director; Department of Roentgenology, E. P. Pendergrass, M.D., Professor; and Department of Otolaryngology, Karl Houser, M.D., Professor.

Fig. 900

THE SPINAL FLUID UNDER PENICILLIN

1. Penicillin (sodium or calcium salt) has not yet been demonstrated in quantity in spinal fluid after intramuscular or intravenous administration. (cf meningitis, Rosenberg and Sylvester 1944)
2. The fact is of no established significance since the good responses are undoubted nonetheless; and it has not been proved that spinal fluid levels even in the arseno-therapeutic era had therapeutic significance.
3. A quantitative Wassermann reaction and total protein estimation are essential to interpretation.
4. The abnormal spinal fluid in late syphilis is improved in 74 per cent of cases of late symptomatic and asymptomatic neurosyphilis. Improvement is marked in 33 per cent.
5. The commonest change is a drop in cell count and total protein in 70 per cent of cases. Both may drop before an eight day course is ended. This is no measure or guide to efficient dose.
6. Relapse likewise begins with a consistent rise in cells or protein.
7. Cell count, protein, Wassermann and colloid tests all improve in 25 per cent of asymptomatic neurosyphilis and 10 per cent of paresis (largely 1,200,000 O.U. dosage)
8. Repeating a course may cause further improvement.
9. Grade III (preparetic) spinal fluids improve and may be reduced to normal after prolonged arsenical and heavy metal therapy has failed.
10. Spinal fluid provocative effects are suspected but not yet clearly demonstrated.
11. Patients with negative bloods and spinal fluids may undergo symptomatic improvement under penicillin.
12. The spinal fluid may remain unchanged despite marked symptomatic improvement.
13. Grade I and II spinal fluids seen in early syphilis usually improve rapidly (ten to fifty days)
14. Even grade III spinal fluid may ultimately be reduced completely to normal by as little as 1,200,000 O.U. in eight days, but such dosage is probably insufficient for routine use.
15. Spinal fluid response after penicillin continues for an unknown period after single course (1,200 000 to 3,000,000 O U)—possibly as long as four months.
16. Hence, in watching progress of neurosyphilis under penicillin, spinal fluid examination should be made not more than one month before and two weeks to one month after penicillin and every two to four months thereafter. A total of six examinations in the first year is advisable.
17. If the spinal fluid fails to improve or standstill after improvement occurs, judged by fluid findings at the fourth to fifth month, the patient should, unless symptomatically worse, be retreated with penicillin, not arsenotherapy. Relapse should be retreated with much larger dosage of penicillin; or fever therapy may be substituted or added.
18. The advisability of substituting penicillin for initial arsenotherapy (Unit courses, pp. 1038, 1049) or for fever in previous untreated cases, should be a matter for individual, if possible consultative decision. If the fluid is grade I or II, after previous treatment, penicillin should certainly be tried before fever and if grade III, it should probably be tried before fever.
19. Previous treatment with As, Bi or fever does not seem to influence the action of penicillin on abnormal spinal fluid.
20. In early syphilis under penicillin (2,400,000 O.U.) examine the spinal fluid early (after penicillin) and at three and six months. If normal at sixth month repeat in one year if possible. If abnormal, retreat with 4,000,000 O.U. and individualize case ... in (1 ...

THESE STATEMENTS ARE AS OF AUGUST 1944—NOT FINAL EVALUATIONS

comitant manifestations such as neurosyphilis. The danger of underdosage is therefore of significance here, and the necessity for complete investigation of the individual with benign late ... from all standpoints, very apparent. In fact, the gummatous late syphilis of the Penicillin Panel Research series yielded a number of cases of concomitant neurosyphilis.

With this statement disposing of the simple problem of benign late syphilis from the symptomatic standpoint, attention should be directed both to the broader delineation of therapeutic

effects on the reagin titer of the blood and on the spinal fluid, both of which, quantitatively studied, supply good indices of the efficiency of penicillin, and the action of penicillin in the more refractory late syphilis of the nervous system, interstitial keratitis, visceral and late congenital syphilis.

The material collected from the Panel clinics for the late syphilis study aggregated 192 cases, and differed from that available in early syphilis, in that no predetermined plan was employed by any investigator and each therefore more or less groped his way into his problem. The aggregate of 192 cases of even limited statistical eligibility had been observed for periods ranging from 8 to 214 days after the institution of treatment. It must be, as in the case of early syphilis, emphasized, iterated and reiterated, therefore, that such material provides only speculative basis for study in many respects and that no final conclusions should be drawn from it. The importance of neurosyphilis in the study is emphasized by the proportion of cases, 122 of neurosyphilis and 60 of other types.

It should also be emphasized that in the late syphilis study the dosage systems so carefully planned in the study of early syphilis have little or no counterpart. No less than 11 different types of treatment appeared in material of 192 cases. This limited any study of treatment effect to comparison of smaller and larger dosages, which gave suggestive but by no means conclusive results, especially qualified in the light of the variability of the observation period.

Fig. 901

SYMPTOMATIC NEUROSYPHILIS UNDER PENICILLIN

1. N eurorecurrences observed thus far
2. Early meningeal eurosyphilis response excellent.
3. Definite Herxheimer effects observed in lat neurosyphilis to be voided by reducing dosage at least one-half for first two to three days. Includes convulsions, myelitic symptoms, etc.
4. Simple dementated paresis, 80 per cent some improvement, 50 per cent improved 50 per cent; 27 per cent improved 75 per cent, 1 complete remission. Encephalogram improves, handwriting may return to normal in six weeks, dysarthria, disorientation, etc., may improve varying degrees up to 100 per cent. Influence of spontaneous remission factor not yet determined.
5. Deteriorated paresis, 33 per cent improved, none put into remission.
6. Tabes dorsalis in the aggregate, 20 per cent improved 50 per cent and more.
   ( ) Lightning pains, severe, one-half improved 50 per cent or more.
   (b) Primary optic atrophy mostly advanced, none made worse, one in seven improved (including spinal fluid).
   ( ) Charcot joint, no response, either preventive or curative.
   (d) Paresthesias, gait, etc., slight improvement.
7 Meningo-vascular neurosyphilis, 40 per cent improve 50 t 75 per cent.
8. Recent ocular nerve palsies (diplopia, ptosis) respond completely if treatment is begun early enough.
9 Optic papillitis and papilledema respond rapidly

Effect of Penicillin Treatment on Blood Serologic Reactions in Late Syphilis.—Penicillin causes reduction of syphilitic reagin titer in the blood in from 50 to 60 per cent of late cases. An initial Herxheimer-like or provocative rise is observed in about 20 per cent of cases. Only five seroresistant cases were treated—one made negative four improved. (See Fig. 899.)

Effect of Penicillin Treatment on the Abnormal Spinal Fluid.—The abnormal spinal fluid in neurosyphilis is improved in 74 per cent of cases in some degree; markedly in 35 per cent. The commonest change is drop in cell count and total protein (rated as grade 2 improvement on scale of five) occurring in 67 per cent of cases. One spinal fluid was rendered normal within the observation period. All four fluid findings improved in 25 per cent of the cases of asymptomatic neurosyphilis, and 10 per cent in paresis and taboparesis. (See Fig 900.)

Symptomatic Improvement in Neurosyphilis.—In simple dementated paresis, of 30 cases on which data were adequate for classification, 80 per cent improved to some degree. Nearly half improved 50 per cent or more, including 8 who improved 75 per cent, and one restored to normal. Deteriorated paresis; two of 10 improved 75 per cent, one 50 per cent, 7 no change. Tabes dorsalis three of 14 cases improved 50 per cent or more; of seven with lightning pains two were completely relieved, one improved 50 per cent, two improved 25 per cent, one remained unchanged

and one became worse. Of seven cases of primary (?) optic atrophy mostly advanced, none was made worse one improved. In meningovascular neurosyphilis, 40 per cent improved from 20 to 75 per cent.

Case Examples in Neurosyphilis.—Since nothing carries conviction to the doubter like the touch of the individual case certain serial spinal fluid and blood findings typical of the best responses observed by the Penicillin Panel groups are reproduced in Figures 902, 904 and 905 For the symptomatic results, two case histories are abstracted (Fig 906) and the improvement in the handwriting of a markedly demented paretic is shown during the six weeks following penicillin through the courtesy of G D Gammon, M D (Fig. 907)

Fig 903.

PENICILLIN PANEL INVESTIGATION

Case 3 (Penna.) Male, age 38, acquired syphilis. Primary optic atrophy in tabes, with euphoria, possible taboparesis. Fields show sector defect suggesting arachnoiditis or retrobulbar neuritic episode. Original spinal fluid, cells 182, Kolmer WR 4444, Pandy 4 plus, mastic 4448110000, improved to cells 29, Kolmer WR 0123, Pandy 3 plus, mastic 4438210000 by 2 Swift Ellis treatments.

Penicillin Treatment Series 1 — Total dose 1,600,000 units

Post penicilli	Quantit. Kline (blood)	Cells	CSF W. (kolmer)	Protein	Mastic
		Cerebrospinal fluid			
0 day	16 unit	29	0123	3 plus	4134110000
13		12	0012	2 plus	2211000000
78	2	10	0112	1 plus	2211000000

Began to lose ground visually with slight confusion and increased euphoria.

Penicillin Treatment Series 2 — Total additional dose 1,800,000

104	16	11	0112	20 mgm.	2211100000
164	Less than 1 unit	5	0012	20 mgm.	2211000000

Definit improvement in fields, acuity and mental stat

It true, of course that these cases put the best foot forward that the permanence of the result is still question and that it is of course difficult t evaluat symptomatology but which elements of the subjective nd the influence of suggestion, rest, practice (in eye station and pupil test) enter but t is clear t le st that penicillin i capable of exerting marked and indeed surprising influence on neurosyphilis of resistant types, including Grade 3 spinal fluid findings. Again, it ca not be expected that penicillin will do the impossible restore lost neurons or do away with scar or t effects.

The Effect of Treatment Systems in Neurosyphilis.—Because of the lack of a uniform plan it was perhaps risky to attempt such a study in a material of this type Two stati tical summations seemed possible however one of the influence of smaller dose as contrasted with larger dose treatment and the other of the response under penicillin of spinal fluids with low as contrasted with relatively high cell counts. None of the results are beyond challenge

They suggest that in late syphilis, especially neurosyphilis, smaller doses, if not grossly inadequate (as in the inadequate 300 000 O U dosage for combined late benign cutaneous and asymptomatic neurosyphilis) may have the good effects of a therapeutic push in the right direction which may perhaps be improved by repetition, as compared with the expected better effects of

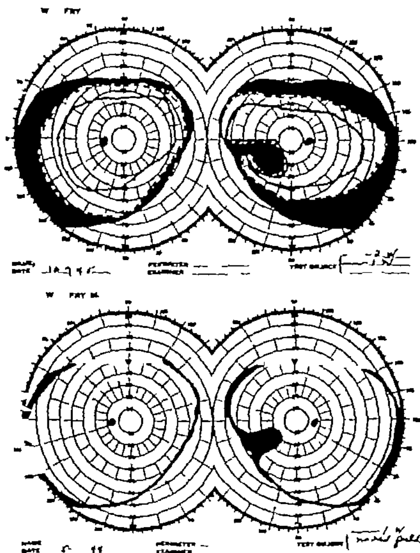


Fig 303.—Visual fields of Case 8, Pennsylvania penicillin series. Improvement with decrease in sector defect shown. Clinical history and spinal fluid findings given in text under above case history number

initial large dosage. It is understood that the term, lower dosage scale, approximates 1,200,000 units, repeated if improvement is delayed or ceases entirely and that 4,000,000 O U represents the larger dosage scale, both being administered in approximately eight to ten days. It is at least suggested that the patient's resistance and defensive responses can be stimulated or utilized by

the lower dosage scale The figures on response in relation to cell count, suggest that moderate to high cell count cases tend to react somewhat better than cases with low cell counts, a conclusion in keeping with experience under the older methods of treatment.

The material studied provided no basis for inferences regarding the combined effect of fever therapy and penicillin or of intrathecal penicillin therapy A breakdown of the material on the basis of the intensity of routine and fever treatment received before penicillin was begun indicated that the good effects of penicillin were obtainable without respect to previous arsenic and heavy metal or indeed of fever therapy

What advice would we offer the practitioner then, confronted with a case of asymptomatic or symptomatic neurosyphilis at the threshold of the penicillin era? Here we believe that the question of individualization is paramount. It is useless to expect responses from dead or gravely damaged structures. It

Fig. 904.

PENICILLIN PANEL INVESTIGATION

Case 11 (Twena.) Male, *age* 18, *congenital syphilis*, discovered at age 6, treated with 30 neoarsphenamine injections a year for 11 years. Typical stigmas, neurologic signs including A-R pupils, anisocoria, partial ptosis left eyelid, weakness left 7th nerve, sluggish reflexes.

Penicillin Treatment Series 1 — Total dose 1,200,000 units

Post penicillin	Quantit. Kline (blood)	Cerebrospinal fluid. Cells.	CSF Wass. (Kolmer)	Protein.	Mastic.
0 days	16 units	32	1244	4 plus	3334410000
13	4	16	0123	1 plus	2111100000
52	4	6	0011	plus-minus	1111000000
140	Less than 1 unit	1	0000	30 mgm.	1110000000

Ptosis disappeared under Penicillin

is equally clear that penicillin produces effects fully equal to the best of preceding chemotherapy It may therefore well be suggested that penicillin in a 4,000,000 O U total dosage be considered eligible treatment for asymptomatic and symptomatic neurosyphilis with the proviso of adequate follow-up, and that such treatment can be substituted for the unit arsenotherapy summarized in Figures 703 704 If the response is not satisfactory fever therapy and not a return to arsenotherapy would seem to be the proper procedure The study of fever in combination with penicillin has just begun, and no opinions on its effectiveness can be offered. Penicillin does not influence the course of therapeutic malaria, so that the combination is usable, even though initial confusion, rather than illumination as to effects is the result to be expected.

Effect of Penicillin in Late Congenital Syphilis.—This is confined almost entirely to the observation of 14 patients with interstitial keratitis who, as previously indicated presented an equivocal though at times dramatically

favorable response. Patients with marked corneal and other ocular damage were included, and too much was expected in the way of results from such material. Of 14 cases, 6 showed improvement—3 of grade 4 on a scale of 1 2, 3 4 one of grade 3, and two of grade 2 Six showed no improvement, and two were definitely worse. When improvement occurred it was apt to be

Fig. 905.

PENICILLIN PANEL INVESTIGATION

Case 40 (Penna.) Male, age 25, congenital syphilis, typical stigmas, asymptomatic neurosyphilis treated with 62 injections neoarsphenamine, 102 injections bismuth.

Penicillin Treatment Series 1 — Total dose 1,200,000 units

Post penicillin.	Quantit. Kline (blood)	Cerebrospinal fluid. Cells.	Wass. (Kolmer)	Protein.	Mastic.
0 days	16 units	96	4444	40 mgm.	2455555421
8	Negative	21	4444	20 mgm.	4442210000
36	32	12	0122	30 mgm.	2221000000

Penicillin Treatment Series 2 — Additional dose 1,200,000 unit

53	Negative	0	0112	30 mgm.	2221100000
84	16	8	0000	20 mgm.	1111000000

Fig 906.

SYMPTOMATIC RESULTS IN TWO PATIENTS WITH NEUROSYPHILIS

U of P 34-W-F-Paresis-symptomatic-Grade III CSF Patient could not write or do housework. Had auditory hallucinations, personality changes, disorientation, tremor of tongue, hands and mouth, slurred speech. On second day of penicillin therapy had Herxheimer reaction with right-sided convulsions becoming generalized. After twenty-four hours, penicillin reinstituted at half dose to total 1,200,000 units without untoward effect. By sixteenth day completely oriented, memory speech, tremor improved, electroencephalogram improved. In four months patient tremor-free, speech and writing normal, well oriented. hallucination-free, and satisfactorily performing housework including marketing with points and driving car Clinical improvement not accompanied by spinal fluid improvement.

J. H. Hosp. 42 M-Paresis-symptomatic. In August, 1943 shell exploded near patient who developed mispronouncing of words, garbled speech, uncertain gait, tremor of hands, difficulty in writing Received 48 arm and hip injections. Became boastful, speech rambling, tremors more pronounced; handwriting worse and calculation poor Unimproved during hospitalization after 50,000 Oxford units per dose of penicillin to 4,000,000 units total. Clinical improvement three weeks post-penicillin with loss of tremors, improved handwriting and speech. Passed examination as pipe fitter CSF did not accompany clinical improvement. Neurologist considered him mentally improved, but not t original level.

dramatic. One patient previously energetically treated with chemotherapy and fever without results was given 1 200,000 O U in eight days. He was relieved of photophobia by the third day and a week after penicillin returned to work for the first time in many months. He has remained well, improvement continuing up to the stage of stationary residue. Another improved grade 4

and 104 days after penicillin flared and recovered again without further treatment. A *persistently seronegative congenital syphilitic with characteristic* stigmas, made no response and in fact became worse under 1,200,000 O U One of McDermott's patients, a fever failure, received a total of 4,845,000 O U in two courses without results. Thomas secured improvement in a case on *4 000 000 O U over 25 days, 20,000 O U every three hours.* Moore has excellent serial color photographs of a favorable case One of his cases likewise improved on 3,970 000 O U in 21 days, observed for 159 days.

Effect of Penicillin on Other Eye Lesions.—Klauder (personal communication) has been able to demonstrate with a slit lamp the Herxheimer effect in a case of syphilitic iritis (not included in this series) Two cases of optic neuritis on 2,000,000 and 3 000 000 O U both showed improvement. O'Leary's case improved 100 per cent on retreatment. Two cases of iritis improved

PENICILLIN

Fig 907 —Improvement in handwriting of simple demented paretic patient approximately n weeks following penicillin treatment. The signature before treatment is given above the word "penicillin. (Courtesy George D Gammon, M.D.)

100 per cent, but one relapsed and required an iridectomy for beginning glaucoma, after failing to respond to retreatment.

What should one say to the eye man confronted with the question of using penicillin in conditions here included? First, if it is possible do all the trying out of other methods of treatment before penicillin is invoked, if the impulse to mix the treatment after penicillin is begun is likely to be irresistible Recall that the eye is a stamping ground for other than specific syphilitic effects, some of which may be favorably influenced by penicillin but others may prove entirely unresponsive if they are not actually made worse Furthermore it should be recalled that it is too early to use penicillin in therapeutic tests for a possible syphilitic factor in all sorts of eye conditions, including otherwise undiagnosed tumors of the orbit and so forth The case should be reasonably clear for syphilis before penicillin is used if it is to be made a basis for the interpretation of penicillin effect.

The Effect of Penicillin on Eighth Nerve Deafness and Visceral Lesions.—This interesting but puzzling problem was left in the air by this investigation. The Ménière syndrome in a congenital syphilitic with eighth nerve deafness failed of improvement. One woman of thirty-one with undoubted stigmas improved definitely but not markedly on 1,200 000 O U Other cases (two in this series) failed to improve. The probabilities are against rather than for a striking good effect in this type of material

Miscellaneous cases permitted the observation of the recedence of a tumor like gummatous mass in the liver under penicillin therapy with equivocal and less definable results in the hepatosplenic complex. Charcot hip failed to respond and a new Charcot joint developed in the patient after penicillin (following injury) Rapidly progressing gangrenous balanitis, always a terror to the therapist and the patient, healed with a loss of less than a third of the corpus spongiosum on 300,000 O U

Herxheimer Effects in Late Syphilis.—It must again be emphasized from this, as from other studies, that penicillin is not a wholly reactionless drug. The disposition to pour it about like water in syphilis may lead to serious trouble especially from therapeutic shock and also from therapeutic paradox ical effect. The former is important under the usual rule that an active syph ilitic process in a vital structure may be gravely and even fatally damaged by the impact of a large dose or series of doses at the start of treatment. Most Herxheimer effects, however seem controllable by reduction in dosage from the first twenty four to forty-eight hours of an eight-day series without loss of ultimate effect. There is some question whether there are not delayed Herx heimer effects such as are suggested by spinal fluid and blood serologic curves, and the initially unfavorable but ultimately favorable course of some lesions (eye nervous system for example)

Of 182 cases, 24 per cent sustained reactions interpretable as Herxheimer or therapeutic shock effect. In four Pennsylvania cases, reactions thus inter preted in the nervous system included transverse myelitic symptoms in one case Jacksonian convulsions lasting twelve hours in another· exacerbation of lightning pains, and mania and hallucinations.

Early Syphilis in Pregnancy

The Penicillin Panel research report by Moore mentioned 58 pregnant women with early syphilis who had been treated but without evaluation of results. This topic was made a special interest of the University of Pennsyl vania group and the subject of a special report. At the deadline for the close of the investigation, 26 cases were collectable from the cooperating clinics includ ing Pennsylvania, with 10 deliveries, 6 at term. The mothers became darkfield negative in four to twelve hours, with 2 mucocutaneous relapses in 12 receiving 600,000 O U and none in 12 receiving 1,200,000 O U to date of close of the investigation Seven of 21 on whom data were available became seronegative within 76 to 148 days.

Of the infants, 10 delivered, all are living, three seronegative on the cord blood at birth, 4 seropositive, and 3 with no data. Five became seronegative under observation 8 of 10 had negative bone roentgenograms. Scrapings of the umbilical vein walls were negative to the darkfield in 5 instances, not per formed in the remainder Figure 908 reproduces the quantitative serologic curves for mother and child in 7 cases, which are part of the group reported by Lentz, Ingraham, Beerman and Stokes from the University of Pennsylvania,

Fig. 308.

SUMMARY OF CLINICAL COURSE OF SEVEN PREGNANT WOMEN WITH EARLY SYPHILIS TREATED WITH PENICILLIN

Symptomatic Clinical Response in the Mother in Each Instance was Immediate

Clinical data.	Days post penicillin.	Mother serologic test. Kline units †	Days after delivery	Infant serologic test. Kline units
Case #4 B-17 yrs. U. of Pa. H.	0	256		
	10	256		
Secondary syphilis	31	64		
Penicillin started 11/19/43	74	64		
Total dose 1,200,000 units	83	8		
	105	64		Negative
Delivered 3/20/44	115	8	0	Negative
	122	32	17	Negative
Infant—weight 6 lbs. 1 oz.	150	4	45	Negative
	175	32	53	Negative
Darkfield umbilical vein negative, normal physical examination. Roentgenogram long bones normal.	207	64	74	Negative
	223	8	101	Negative
Case #13 B-29 yrs. P. G. H.				
Secondary syphilis	0	128		
Penicillin started 12/16/43	2	128		
Total dose 1,200,000 units	26	32		
	65	16		
Delivered 3/29/44	80	2		
	104	4	0	0.5
Infant—weight 6 lbs. 2½ oz.	124	16	20	Negative
	141	Negative	37	Negative
Darkfield umbilical vein negative, normal physical examination. *Roentgenogram long bones normal.*	159	Negative	55	Negative
	173	0.5	60	Negative
			85	Negative
Case #15 B-16 yrs. Pa. H.	0	128		
	10	64		
Secondary syphil'	25	128		
Penicillin started 12/24/43	30	32		
Total dose 1,200,000 units	60	32		
	74	16		
Delivered 5/18/44	87	4		
	115	0.5		
Infant—weight 6 lbs. 11 oz.	122	Negative		
	136	Negative	0	Negative
Darkfield umbilical vein negative, normal physical examination.	143	Negative	25	Negative
	168	Negative		
Case #25 B-19 yrs. U. of Pa. H.				
	0	128		
Secondary syphilis	16	64		
Penicillin started 1/10/44	20	64		
Total dose 1,200,000 units	53	64		
	65	16		
Delivered 4/15/44	79	32		16
	91	32	0	4
Infant—weight 6 lbs. 14½ oz.	105	32	9	Negative
	114	Negative	20	Negative
Darkfield, umbilical vein negative, normal physical examination. Roentgenogram long bones normal.	128	2	34	Negative
	145	4	54	Negative
	165	Negative	60	

Material from paper by Lentz, Ingraham, Beerman and Stokes, J.A.M.A. to be published.

† Given in Kline units for sake of uniformity. Tests were checked with quantitative Kolmer Wassermann and Eagle flocculation with comparable results.

Fig. 908 (*Continued*)

SUMMARY OF CLINICAL COURSE OF SEVEN PREGNANT WOMEN WITH EARLY SYPHILIS TREATED WITH PENICILLIN

Symptomatic Clinical Response in the Mother in Each Instance was Immediate

Clinical data.	Days post penicillin.	Mother serologic test. Kline units.†	Days after delivery	Infant serologic test. Kline units.
Case #40 B-21 yrs. U. of Pa. H.				
Secondary syphilis	0	64		
Penicillin started 2/15/44	8	64		
Total dose: 2,400,000 units	21	128		
	36	64		
Delivered 4/3/44	43	64	0	64
	49		1	16
Infant—weight 6 lbs. 5½ oz.	77	64	29	Negative
	88	32	40	Negative
Darkfield umbilical vein negative, normal physical examination. Roentgenogram long bones normal.	112	8	64	Negative
	126	2	78	Negative
Case #71 B-22 yrs. U of Pa. H.				
	0	128		
Early latent syphilis	14	64		
Penicillin started 3/31/44	23	128		
Total dose. 1,500,000 units	44	32		
	60	32		
Delivered 6/14/44	76	64	0	Negative
	77		1	0 25
Infant—weight 5 lbs. ¼ oz. Normal physical examination.				
Case #70 B-24 yrs. P.G.H.				
Secondary syphilis	0	64		
Penicillin started 4/5/44	13	128		
Total dose: 1,200,000 units	27	64		
	41	64		
Delivered 6/17/44	54	32		
	60	64		
Infant—weight 4 lbs. 10¼ oz. Normal physical examination.	73	64	0	Negative

observed for the longest period. It is too early to judge whether the mothers who were not seronegative at the time of delivery will ultimately become so or not. Observation since the deadline rather tends to suggest that there is a distinct tendency in the mother's curve to rise following the delivery as if the child had had, so to speak, while *in utero*, an inhibitive effect. There seems little or no question of the high degree of protection afforded to the child, which has been after all, the chief objective of the treatment of syphilis in pregnancy in the arsenical era. Under conditions almost certain to result in infection of the child *in utero*, had penicillin been ineffective, not a single miscarriage, stillbirth or clinically syphilitic infant resulted. Of course, only prolonged observation will establish clearly the absence of the disease in the mothers or the infants who have become seronegative after birth, or who are seronegative at the time of birth. The roentgenographic confirmation of the freedom of these children from syphilis is of almost greater weight than their serologic findings, and makes the outlook, so far as the child is concerned, quite promising Since the dosage employed, 1,200 000 units at 25 000 units

over 4 hours (the dose being reduced in the first twenty four to forty-eight hours as a result of our observation of two cases of threatened abortion on maximum dosage) is, in the light of our present conceptions in the treatment of early syphilis, probably inadequate for the cure of the mother in the highest possible proportion of cases even though it may protect the child, it should be advanced to 2 400 000 O U and patients who have received 1,200,000 O.U should unless clearly and lastingly seronegative, be retreated with the larger dosage

It should be noted that the earliest cases do not include as yet (a) latent syphilitic mothers, (b) pregnancies in which treatment was begun before the fifth month. The permeability of the placenta to penicillin is still undetermined Barksdale reported failure to find penicillin in the cord blood in 3 cases (J.A.M.A. in discussion) in which the mother was given a large dose intravenously at the time of delivery but a small amount was found in a subsequent case (personal communication)

INFANTILE CONGENITAL SYPHILIS

Nine congenitally syphilitic infants were treated by the University of Pennsylvania group Three have been followed long enough (99 97 70 days) to

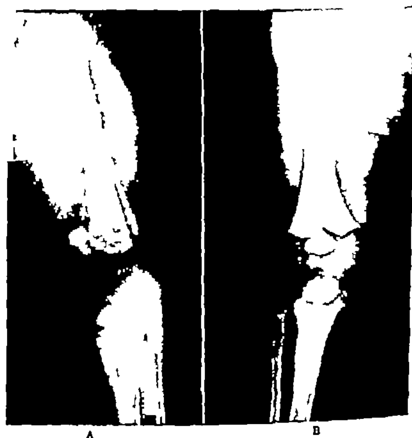


Fig 909 —A, Before penicillin. B, After penicillin

show the type of clinical and serologic response which may be obtained (Fig 908) They may well be rated remarkable. The two infants who showed defaulte

roentgenographic changes of osteochondritis and periostitis resumed normal bone development (Fig 909)

The total dosage employed in 6 of the 9 infants ranged from 13,000 to 16 000 O U per pound (28,600 and 34,200 O U per kilo respectively) given intramuscularly in fractions at four hour intervals, round the clock for eight days. After observing one supposedly Herxheimer reaction at 19 000 O U in the first forty-eight hours (cyanosis, dyspnea, nasorespiratory tract obstruction) the practice of using half doses for the first forty-eight hours seemed advisable and there is good reason to believe that a longer reduction period would be desirable in gravely diseased infants. Lentz, Ingraham, Beerman and Stokes strongly urge the need for expert pediatric care of the infant regardless of the apparently good general tolerance of penicillin exhibited in their series Two deaths were the result of medical complications (congenital heart, infectious diarrhea) not the penicillin.

The Most Recent Penicillin Panel Results in Early Syphilis

We are deeply indebted to Dr J E. Moore and the Penicillin Panel of the National Research Council for the opportunity to present here in advance of publication in the literature, the latest tabulations prepared by Moore, cover

Fig. 910.

GROSS OVERALL RESULTS OF PENICILLIN IN EARLY SYPHILIS
(As of August 1 1944)

Total dose of penicillin (units) intramuscularly	Duration of treatment (days).	Total cases treated.	Maximum observation period (days)	Treatment failures.	Gross percentage failure (these figures meaningless except for comparison)
60,000	7½	31	294	15	48 4
300,000	7½	306	290	34	11 1
600,000	7½	673	294	23	3 4
1,200,000	7½	483	250	10	2 0
2,400,000	7½	100	112		
60,000 and 320 mg. mapharsen	7½	45	185	3	6 6
300,000 and 320 mg. mapharsen	7½	114	140	3	2 6
Penicillin Intravenously					
1 1.2 million	5–6	29		4	13 8
300,000	4	41	56		
600,000	4	101	112		
1,200,000	4	107	112	1	
2,400,000	4	39	42		
Total Cases Treated		2072			

ing penicillin treatment results in early syphilis as of August 1 1944 To quote Moore s explanatory letter

"Figure 910 is of value only in showing (1) the total number of cases so far treated in each dosage group, (2) the probable (but not yet proved) advantage of penicillin plus mapharsen, especially in the 300,000 unit group, (3) the cases treated in four days with as yet too short observation periods for any results, (4) the probable (but not yet proved) disadvantages of the intravenous route, and (5) the absolute inadequacy of 60,000 units total dose.

*Figure 911 is the one which really counts. Enough cases and elapsed observation time are available in only three groups t permit figuring cumulative percentages, and in them only to the 140th day after treatment. The maximum observation periods in the three dosage groups tabulated (and others) are shown in Fig. 910, but the number followed after the 140th day is as yet too small for statistical significance. In Figure 911 the final column is only a guess, but may be a good one.

Fig. 911

PRELIMINARY RESULTS IN EARLY SYPHILIS OF 60 INTRAMUSCULAR INJECTIONS OF PENICILLIN GIVEN EVERY 3 HOURS FOR 7½ DAYS

(As of August 1 1944)

Total dose of penicillin (units)	Number cases treated.	Number cases followed 115–140 days.	Cumulative per cent failure 115–140 days.	Cumulative per cent becoming seronegative 115–140 days.	Cases failing after 140 days.	Probable eventual cumulative per cent failure.
300,000	306	65	26.1 (17 failures)	48.4	7	60
600,000	673	95	13.4 (10 failures)	57.4	4	20–30
1,200,000	495	77	7.6 (5 failures)	71.8	2	10–15

Gross number followed too small to permit percentages.

The reinforcing power of mapharsen in lower total doses of penicillin should be borne in mind where the amount of penicillin available is limited by any circumstances and might even be considered as reinforcement at the low dosage employed for the penicillin therapy of gonorrhea reasonably suspected of being likely to mask a coincident syphilis, as in some conditions prevailing among the armed forces in some theaters, especially the Orient. The excellent record of 1 200 000 O U encourages the hope that 2,400,000 O U will leave a negligible margin of relapse in early syphilis.

INDEX